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(71) Applicant *(for all designated States except US)*: DOW AGROSCIENCES LLC [US/US]; 9330 Zionsville Road, Indianapolis, IN 46268 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BALTZ, Richard, H. [US/US]; 6438 North Olney Road, Indianapolis, IN 46220 (US). BROUGHTON, M., Christine [US/US]; 5430 Central Avenue, Indianapolis, IN 46220 (US). CRAWFORD, Kathryn, P. [US/US]; 432 North Riley Avenue, Indianapolis, IN 46201 (US). MADDURI, Krishnamurthy [US/US]; 31 Towne Commons West, Woodlawn, OH 45215 (US). MERLO, Donald, J. [US/US]; 11845 Durbin Drive, Carmel, IN 46032 (US). TREADWAY, Patti, J. [US/US]; 4268 West Fox Ridge Avenue, Greenwood, IN 46143 (US). TURNER, Jan, R. [US/US]; 651 Ash Drive, Carmel, IN 46032 (US). WALDRON, Clive [US/US]; 6206 Green Leaves Road, Indianapolis, IN 46220 (US).

(74) Agent: STUART, Donald, R.; 9330 Zionsville Road, Indianapolis, IN 46268 (US).

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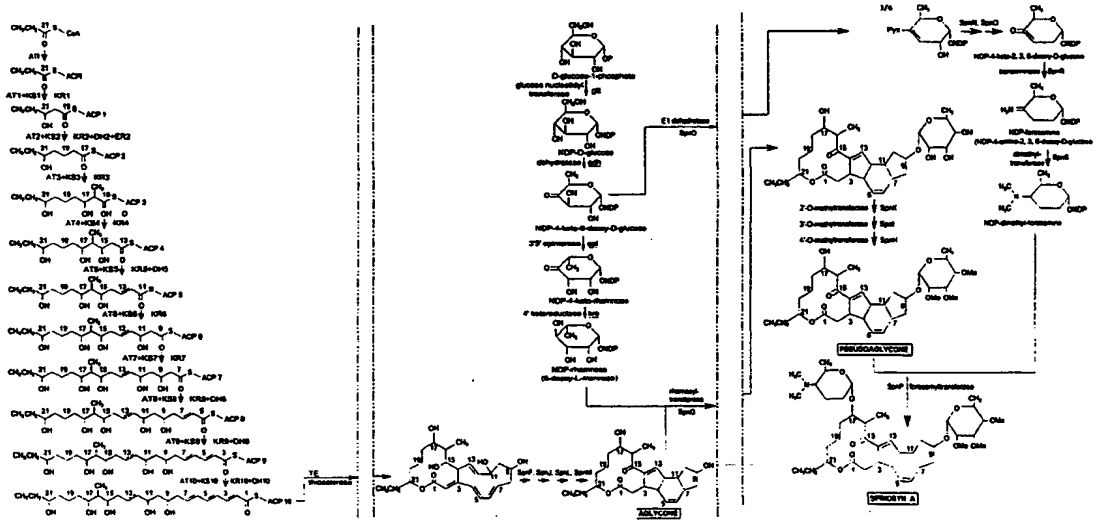
(54) Title: BIOSYNTHETIC GENES FOR SPINOSYN INSECTICIDE PRODUCTION



(57) Abstract

Spinosyn biosynthetic genes, spinosyn producing microorganisms transformed with the biosynthetic genes, methods using the biosynthetic genes to increase production of spinosyn insecticidal macrolides, and methods using the genes or fragments thereof to change the products produced by spinosyn–producing microorganisms.

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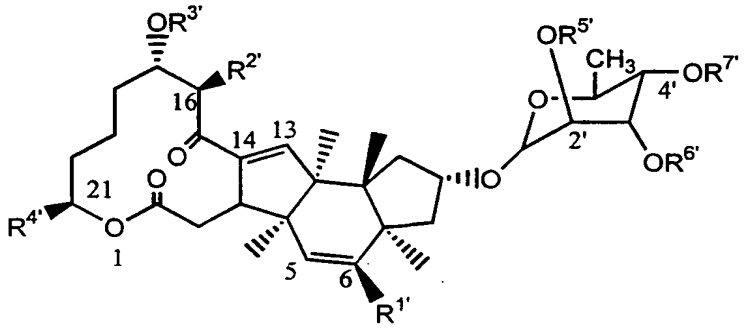
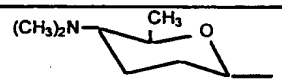
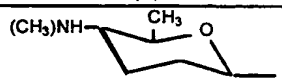
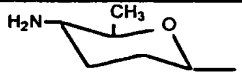
BIOSYNTHETIC GENES FOR SPINOSYN INSECTICIDE PRODUCTION

The present invention provides novel biosynthetic genes, vectors incorporating the biosynthetic genes, *Saccharopolyspora spinosa* strains transformed with the biosynthetic genes, methods using these genes to increase production of spinosyn insecticidal macrolides, and methods using the genes or fragments thereof to change the products produced by spinosyn-producing strains of *Saccharopolyspora spinosa*.

As disclosed in US Patent No. 5,362,634, fermentation product A83543 is a family of related compounds produced by *Saccharopolyspora spinosa*. The known members of this family have been referred to as factors or components, and each has been given an identifying letter designation. These compounds are hereinafter referred to as spinosyn A, B, etc. The spinosyn compounds are useful for the control of arachnids, nematodes and insects, in particular *Lepidoptera* and *Diptera* species, and they are quite environmentally friendly and have an appealing toxicological profile. Tables 1 and 2 identify the structures of a variety of known spinosyn compounds:

Table 1



Factor	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	$R^{6'}$	$R^{7'}$
spinosyn A	H	CH_3	 (a)	C_2H_5	CH_3	CH_3	CH_3
spinosyn B	H	CH_3	 (b)	C_2H_5	CH_3	CH_3	CH_3
spinosyn C	H	CH_3	 (c)	C_2H_5	CH_3	CH_3	CH_3
spinosyn D	CH_3	CH_3	(a)	C_2H_5	CH_3	CH_3	CH_3
spinosyn E	H	CH_3	(a)	CH_3	CH_3	CH_3	CH_3
spinosyn F	H	H	(a)	C_2H_5	CH_3	CH_3	CH_3

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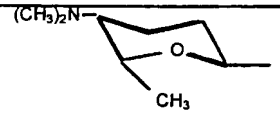
Factor	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	$R^{6'}$	$R^{7'}$
spinosyn G	H	CH_3	 (d)	C_2H_5	CH_3	CH_3	CH_3
spinosyn H	H	CH_3	(a)	C_2H_5	H	CH_3	CH_3
spinosyn J	H	CH_3	(a)	C_2H_5	CH_3	H	CH_3
spinosyn K	H	CH_3	(a)	C_2H_5	CH_3	CH_3	H
spinosyn L	CH_3	CH_3	(a)	C_2H_5	CH_3	H	CH_3
spinosyn M	H	CH_3	(b)	C_2H_5	CH_3	H	CH_3
spinosyn N	CH_3	CH_3	(b)	C_2H_5	CH_3	H	CH_3
spinosyn O	CH_3	CH_3	(a)	C_2H_5	CH_3	CH_3	H
spinosyn P	H	CH_3	(a)	C_2H_5	CH_3	H	H
spinosyn Q	CH_3	CH_3	(a)	C_2H_5	H	CH_3	CH_3
spinosyn R	H	CH_3	(b)	C_2H_5	H	CH_3	CH_3
spinosyn S	H	CH_3	(a)	CH_3	H	CH_3	CH_3
spinosyn T	H	CH_3	(a)	C_2H_5	H	H	CH_3
spinosyn U	H	CH_3	(a)	C_2H_5	H	CH_3	H
spinosyn V	CH_3	CH_3	(a)	C_2H_5	H	CH_3	H
spinosyn W	CH_3	CH_3	(a)	C_2H_5	CH_3	H	H
spinosyn Y	H	CH_3	(a)	CH_3	CH_3	CH_3	H
spinosyn A 17-Psa	H	CH_3	H	C_2H_5	CH_3	CH_3	CH_3
spinosyn D 17-Psa	CH_3	CH_3	H	C_2H_5	CH_3	CH_3	CH_3
spinosyn E 17-Psa	H	CH_3	H	CH_3	CH_3	CH_3	CH_3
spinosyn F 17-Psa	H	H	H	C_2H_5	CH_3	CH_3	CH_3
spinosyn H 17-Psa	H	CH_3	H	C_2H_5	H	CH_3	CH_3
spinosyn J 17-Psa	H	CH_3	H	C_2H_5	CH_3	H	CH_3
spinosyn L 17-Psa	CH_3	CH_3	H	C_2H_5	CH_3	H	CH_3

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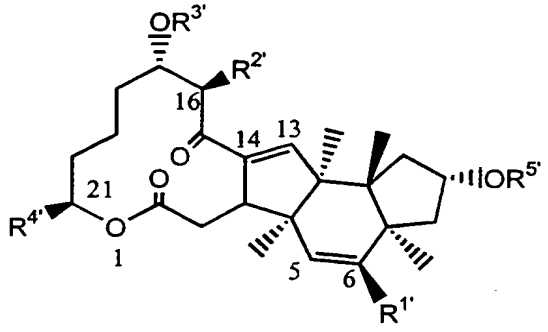
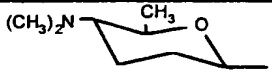
Table 2



Factor	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
spinosyn A 9-Psa	H	CH_3	 (a)	C_2H_5	H
spinosyn D 9-Psa	CH_3	CH_3	(a)	C_2H_5	H
spinosyn A Aglycone	H	CH_3	H	C_2H_5	H
spinosyn D Aglycone	CH_3	CH_3	H	C_2H_5	H

The naturally produced spinosyn compounds consist of a 5,6,5-tricylic ring system, fused to a 12-membered macrocyclic lactone, a neutral sugar (rhamnose) and an amino sugar (forosamine) (see Kirst *et al.* (1991). If the amino sugar is not present the compounds have been referred to as the pseudoaglycone of A, D, etc., and if the neutral sugar is not present then the compounds have been referred to as the reverse pseudoaglycone of A, D, etc. A more preferred nomenclature is to refer to the pseudoaglycones as spinosyn A 17-Psa, spinosyn D 17-Psa, etc., and to the reverse pseudoaglycones as spinosyn A 9-Psa, spinosyn D 9-Psa, etc.

The naturally produced spinosyn compounds may be produced via fermentation from cultures NRRL 18395, 18537, 18538, 18539, 18719, 18720, 18743 and 18823. These cultures have been deposited and made part of the stock culture collection of the Midwest Area Northern Regional Research Center, Agricultural Research Service, United States Department of Agriculture, 1815 North University Street, Peoria, IL 61604.

U. S. Patent No. 5,362,634 and corresponding European Patent Application No. 375316 A1 disclose spinosyns A, B, C, D, E, F, G, H, and J. These compounds

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are disclosed as being produced by culturing a strain of the novel microorganism *Saccharopolyspora spinosa* selected from NRRL 18395, NRL 18537, NRRL 18538, and NRRL 18539.

WO 93/09126 disclosed spinosyns L, M, N, Q, R, S, and T. Also disclosed therein are two spinosyn J producing strains: NRRL 18719 and NRRL 18720, and a strain that produces spinosyns Q, R, S, and T: NRRL 18823.

WO 94/20518 and US 5,6704,486 disclose spinosyns K, O, P, U, V, W, and Y, and derivatives thereof. Also disclosed is spinosyn K-producing strain NRRL 18743.

A challenge in producing spinosyn compounds arises from the fact that a very large fermentation volume is required to produce a very small quantity of spinosyns. It is highly desired to increase spinosyn production efficiency and thereby increase availability of the spinosyns while reducing their cost. A cloned fragment of DNA containing genes for spinosyn biosynthetic enzymes would enable duplication of genes coding for rate limiting enzymes in the production of spinosyns. This could be used to increase yield in any circumstance when one of the encoded activities limited synthesis of the desired spinosyn. A yield increase of this type was achieved in fermentations of *Streptomyces fradiae* by duplicating the gene encoding a rate-limiting methyltransferase that converts macrocin to tylosin (Baltz *et al.*, 1997). In another example, WO 97/06266 shows insertion of a second copy of ery G into a nonessential region of the Sac. erythraea chromosome to improve conversion of 6-deoxyerythromycin D to 6,12-dideoxyerythromycin A.

Cloned biosynthetic genes would also provide a method for producing new derivatives of the spinosyns which may have a different spectrum of insecticidal activity. New derivatives are desirable because, although known spinosyns inhibit a broad spectrum of insects, they do not control all pests. Different patterns of control may be provided by biosynthetic intermediates of the spinosyns, or by their derivatives produced *in vivo,* or by derivatives resulting from their chemical modification *in vitro*. Specific intermediates (or their natural derivatives) could be synthesized by mutant strains of *S. spinosa* in which certain genes encoding enzymes for spinosyn biosynthesis have been disrupted. Such strains can be generated by integrating, via homologous recombination, a mutagenic plasmid containing an

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internal fragment of the target gene. Upon plasmid integration, two incomplete copies of the biosynthetic gene are formed, thereby eliminating the enzymatic function it encoded. The substrate for this enzyme, or some natural derivative thereof, should accumulate upon fermentation of the mutant strain. Such a strategy was used effectively to generate a strain of *Saccharopolyspora erythraea* producing novel 6-deoxyerythromycin derivatives (Weber & McAlpine, 1992).

Novel intermediates could also be synthesized by mutant strains of *S. spinosa* in which parts of certain genes encoding enzymes for spinosyn biosynthesis have been replaced with parts of the same gene which have been specifically mutated *in vitro*, or with corresponding parts of genes from other organisms. Such strains could be generated by swapping the target region, via double homologous recombination, with a mutagenic plasmid containing the new fragment between non-mutated sequences which flank the target region. The hybrid gene would produce protein with altered functions, either lacking an activity or performing a novel enzymatic transformation. A new derivative would accumulate upon fermentation of the mutant strain. Such a strategy was used to generate a strain of *Saccharopolyspora erythraea* producing a novel anhydroerythromycin derivative (Donadio *et al.*, 1993). The nucleic acids of the invention can be used in production of engineered polyketide synthases of the type disclosed in WO 93/13663 and US 5,824,513, in production of hybrid polyketide synthases of the type described in and WO 98/01546, WO 98/49315, and WO98/51695, and in construction of polyketide synthase libraries and polyketide libraries as described in WO 96/40968, WO 98/49315, WO 98/27203, US 5,783,431, US 5,824,485, and US 5,811,238.

Biosynthesis of spinosyns proceeds via stepwise condensation and modification of 2- and 3-carbon carboxylic acid precursors, generating a linear polyketide that is cyclized and bridged to produce the tetracyclic aglycone. Pseudoaglycone (containing tri-O-methylated rhamnose) is formed next, then di-N-methylated forosamine is added to complete the biosynthesis (Broughton *et al.*, 1991). Other macrolides, such as the antibiotic erythromycin, the antiparasitic avermectin and the immunosuppressant rapamycin, are synthesized in a similar fashion. In the bacteria producing these compounds, most of the macrolide biosynthetic genes are clustered together in a 70-80 kb region of the genome (Donadio *et al.*, 1991; MacNeil

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et al., 1992; Schwecke *et al.*, 1995). At the centers of these clusters are 3-5 highly conserved genes coding for the very large, multifunctional proteins of a Type I polyketide synthase (PKS). Together the polypeptides form a complex consisting of an initiator module and several extender modules, each of which adds a specific acyl-CoA precursor to a growing polyketide chain, and modifies the β-keto group in a specific manner. The structure of a polyketide is therefore determined by the composition and order of the modules in the PKS. A module comprises several domains, each of which performs a specific function. The initiator module consists of an acyl transferase (AT) domain for addition of the acyl group from the precursor to an acyl carrier protein (ACP) domain. The extender modules contain these domains, along with a β-ketosynthase (KS) domain that adds the pre-existing polyketide chain to the new acyl-ACP by decarboxylative condensation. Additional domains may also be present in the extender modules to carry out specific β-keto modifications: a β-ketoreductase (KR) domain to reduce the β-keto group to a hydroxyl group, a dehydratase (DH) domain to remove the hydroxyl group and leave a double bond, and an enoyl reductase (ER) domain to reduce the double bond and leave a saturated carbon. The last extender module terminates with a thioesterase (TE) domain that liberates the polyketide from the PKS enzyme in the form of a macrocyclic lactone.

Macrolides are derived from macrocyclic lactones by additional modifications, such as methylation and changes in reductive state, and the addition of unusual sugars. Most of the genes required for these modifications, and for the synthesis and attachment of the sugars, are clustered around the PKS genes. The genes encoding deoxysugar biosynthetic enzymes are similar in producers of macrolide antibiotics, such as erythromycin and tylosin (Donadio *et al.*, 1993; Merson-Davies & Cundliffe, 1994), and producers of extracellular polysaccharides, such as the O-antigens of *Salmonella* and *Yersinia* (Jiang *et al.*, 1991; Kessler *et al.*, 1993). All these syntheses involve activation of glucose by the addition of a nucleotide diphosphate, followed by dehydration, reduction and/or epimerization. The resultant sugar could undergo one or more modifications such as deoxygenation, transamination and methylation, depending upon the type of sugar moiety present in the macrolide. The sugars are incorporated into macrolides by the action of specific glycosyltransferases. Genes involved in the synthesis and attachment of a sugar may be tightly clustered - even

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transcribed as a single operon - or they may be dispersed (Decker & Hutchinson, 1993; Jarvis & Hutchinson, 1994). Spinosyn synthesis also involves bridging of the lactone nucleus, an activity that is rare in macrolide producers. Therefore, the spinosyn biosynthetic cluster may uniquely contain additional genes encoding enzymes for this function.

The following terms are used herein as defined below:

AmR - the apramycin resistance-conferring gene.

ApR - the ampicillin resistance-conferring gene.

ACP - acyl carrier protein.

AT - acyltransferase.

bp - base pairs.

Cloning - the process of incorporating a segment of DNA into a recombinant DNA cloning vector and transforming a host cell with the recombinant DNA.

CmR - the chloramphenicol resistance-conferring gene.

Codon bias - the propensity to use a particular codon to specify a specific amino acid. In the case of *S. spinosa*, the propensity is to use a codon having cytosine or guanine as the third base.

Complementation - the restoration of a mutant strain to its normal phenotype by a cloned gene.

Conjugation - a process in which genetic material is transferred from one bacterial cell to another.

cos - the lambda cohesive end sequence.

Cosmid - a recombinant DNA cloning vector which is a plasmid that not only can replicate in a host cell in the same manner as a plasmid but also can be packaged into phage heads.

DH - dehydratase.

ER - enoyl reductase.

Exconjugant - recombinant strain derived from a conjugal mating.

Gene - a DNA sequence that encodes a polypeptide.

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Genomic Library - a set of recombinant DNA cloning vectors into which segments of DNA, representing substantially all DNA sequences in a particular organism have been cloned.

Homology - degree of similarity between sequences

Hybridization - the process of annealing two single stranded DNA molecules to form a double stranded DNA molecule, which may or may not be completely base paired.

In vitro packaging - the *in vitro* encapsulation of DNA in coat protein to produce a virus-like particle that can introduce DNA into a host cell by infection

kb - kilo base pairs.

KR - β-keto reductase.

KS - ketosynthase.

Mutagenesis - creation of changes in DNA sequence. They can be random or targeted, generated *in vivo* or *in vitro*. Mutations can be silent, or can result in changes in the amino acid sequence of the translation product which alter the properties of the protein and produce a mutant phenotype.

NmR - the neomycin resistance-conferring gene.

ORF - open reading frame.

ori - a plasmid origin of replication (oriR)or transfer (oriT).

PKS - polyketide synthase.

Promoter - a DNA sequence that directs the initiation of transcription.

Recombinant DNA cloning vector - any autonomously replicating or integrating agent, including , but not limited to, plasmids, comprising a DNA molecule to which one or more additional DNA molecules can be or have been added.

Recombinant DNA methodology - technologies used for the creation, characterization, and modification of DNA segments cloned in recombinant DNA vectors.

Restriction fragment - any linear DNA molecule generated by the action of one or more restriction enzymes.

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Spinosyn - a fermentation product typically characterized by a 5,6,5-tricylic ring system, fused to a 12-membered macrocyclic lactone, a neutral sugar (rhamnose) and an amino sugar (forosamine), or a similar macrocyclic lactone fermentation product produced by a microorganism utilizing all or most of the spinosyn genes.

Spinosyn genes- the DNA sequences that encode the products required for spinosyn biosynthesis, more specifically the genes *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, and *S. spinosa kre*, as described hereinafter, or functional equivalents thereof.

Subclone - a cloning vector with an insert DNA derived from another DNA of equal size or larger.

TE - thioesterase.

Transformation - the introduction of DNA (heterologous or homologous) into a recipient host cell that changes the genotype and results in a change in the recipient cell.

Brief Description of the Figures

FIG. 1 is a diagram illustrating the spinosyn biosynthetic pathway.

FIG. 2 is a map illustrating the arrangement of *Bam*HI fragments and open reading frames in the cloned region of *S. spinosa* DNA.

FIG. 3 is a restriction site and functional map of Cosmid pOJ436.

FIG. 4 is a restriction site and functional map of Cosmid pOJ260.

FIG. 5 is a restriction site and functional map of pDAB 1523.

Brief Description of the Invention

Spinosyn biosynthetic genes and related ORFs were cloned and the DNA sequence of each was determined. The cloned genes and ORFs are designated hereinafter as *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, ORFL15, ORFL16, ORFR1, ORFR2, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, and *S. spinosa kre*. The

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proposed functions of the cloned genes in spinosyn biosynthesis are identified FIG. 1 and in the discussion hereinafter.

In one of its aspects, the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn biosynthetic enzyme, wherein said enzyme is defined by an amino acid sequence selected from the group consisting of SEQ ID NOS 2-5, 7-24, 26, 27, 29, and 33, or said enzyme is defined by one of said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the encoded enzyme. In a preferred embodiment, the DNA sequence is selected from the group of genes consisting of *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, ORFL15, ORFL16, ORFR1, ORFR2, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, and *S. spinosa kre*, said genes being described by, respectively, bases 21111-28898, 28916-35374, 35419-44931, 44966-59752, 59803-76569, 20168-20995, 18541-19713, 17749-18501, 16556-17743, 14799-16418, 13592-14785, 12696-13547, 11530-12492, 10436-11434, 8967-10427, 7083-8450, 5363-6751, 4168-5325, 3416-4165, 2024-2791, 1135-1971, 76932-77528 and 77729-79984 of SEQ ID NO:1, bases 334-1119 of SEQ ID NO:27, bases 88-1077 of SEQ ID NO 24, bases 226-834 of SEQ ID NO 31, and bases 1165-1992 of SEQ ID NO:24.

In another of its aspects, the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain selected from KSi, ATi, ACPi, KS1, AT1, KR1, and ACP1, said domains being described by, respectively, amino acids 6-423, 528-853, 895-977, 998-1413, 1525-1858, 2158-2337, and 2432-2513 of SEQ ID NO:2. In a preferred embodiment, the DNA sequence is selected from the group consisting of bases 21126-22379, 22692-23669, 23793-24041, 24102-25349, 25683-26684, 27582-28121, and 28404-28649 of SEQ ID NO:1.

In another of its aspects, the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain selected from KS2, AT2, DH2, ER2, KR2, and ACP2, said domains being described by, respectively, amino acids 1-424, 536-866, 892-1077, 1338-1683, 1687-1866, and 1955-2034 of

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SEQ ID NO:3. In a preferred embodiment the DNA sequence is selected from the group consisting of bases 29024-30295, 30629-31621, 31697-32254, 33035-34072, 34082-34621, 34886-35125 of SEQ ID NO:1.

In another of its aspects, the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain selected from KS3, AT3, KR3, ACP3, KS4, AT4, KR4, and ACP4, said domains being described by, respectively, amino acids 1-423, 531-280, 1159-1337, 1425-1506, 1529-1952, 2066-2396, 2700-2880, and 2972-3053 of SEQ ID NO:4. In a preferred embodiment the DNA sequence is selected from the group consisting of bases 35518-36786, 37108-38097, 38992-39528, 39790-40035, 40102-41373, 41713-42705, 43615-44157, and 44431-44676 of SEQ ID NO:1.

In another of its aspects the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain selected from KS5, AT5, DH5, KR5, ACP5, KS6, AT6, KR6, ACP6, KS7, AT7, KR7, and ACP7, said domains being described by, respectively, amino acids 1-424, 539-866, 893-1078, 1384-1565, 1645-1726, 1748-2172, 2283-2613, 2916-3095, 3188-3269, 3291-3713, 3825-4153, 4344-4638, and 4725-4806 of SEQ ID NO:5. In a preferred embodiment the DNA sequence is selected from the group consisting of bases 45077-46348, 46691-47674, 47753-48310, 49226-49771, 50009-50254, 50318-51592, 51923-52915, 53822-54361, 54638-54883, 54947-56215, 56549-57535, 58106-58990, and 59249-59494 of SEQ ID NO:1.

In another of its aspects, the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain selected from KS8, AT8, DH8, KR8, ACP8, KS9, AT9, DH9, KR9, ACP9, KS10, AT10, DH10, KR10, ACP10, and TE10, said domains being described by, respectively, amino acids 1-424, 530-848, 883-1070, 1369-1552, 1648-1726, 1749-2173, 2287-2614, 2640-2800, 3157-3341, 3422-3500, 3534-3948, 4060-4390, 4413-4597, 4900-5078, 5172-5253, and 5302-5555 of SEQ ID NO:6. In a preferred embodiment, the DNA sequence is selected from the group consisting of bases 59902-61173, 61489-62445, 62548-63111, 64006-64557, 64843-65079, 65146-66420, 66760-67743, 67819-68301, 69370-69924, 70165-70401, 70471-71745, 72079-73071, 73138-73692, 74599-75135, 75415-75660, and 75805-76566 of SEQ ID NO:1.

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In another of its aspects the invention provides an isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS module, said module being selected from the group consisting of amino acids 6-1413 of SEQ ID NO:2, 1525-2513 of SEQ ID NO:2, 1-2034 of SEQ ID NO:3, 1-1506 of SEQ ID NO:4, 1529-3053 of SEQ ID NO:4, 1-1726 of SEQ ID NO:5, 1748-3269 of SEQ ID NO:5, 3291-4806 of SEQ ID NO:5, 1-1726 of SEQ ID NO:5, 1-1726 of SEQ ID NO:6, 1749-3500 of SEQ ID NO:6, and 35434-5555 of SEQ ID NO:6. In a preferred embodiment the DNA sequence is selected from the group consisting of bases 21126-24041, 24102-28649, 29024-35125, 35518-40035, 40102-44676, 45077-50254, 50318-54883, 54947-59494, 59902-65079, 65146-70401, and 70471-76566 of SEQ ID NO:1.

In another of its aspects, the invention provides a recombinant DNA vector which comprises a DNA sequence of the invention as described above.

In another of its aspects the invention provides a host cell transformed with a recombinant vector of the invention as described above.

In another of its aspects, the invention provides a method of increasing the spinosyn-producing ability of a spinosyn-producing microorganism comprising the steps of

1) transforming with a recombinant DNA vector or portion thereof a microorganism that produces spinosyn or a spinosyn precursor by means of a biosynthetic pathway, said vector or portion thereof comprising a DNA sequence of the invention, as described above, that codes for the expression of an activity that is rate limiting in said pathway, and

2) culturing said microorganism transformed with said vector under conditions suitable for cell growth and division, expression of said DNA sequence, and production of spinosyn.

In another of its aspects the invention provides a spinosyn-producing microorganism having operative spinosyn biosynthetic genes wherein at least one of the spinosyn biosynthetic genes *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, or *S. spinosa kre* has been duplicated.

In another of its aspects the invention provides a spinosyn-producing microorganism, said microorganism having spinosyn biosynthetic genes in its

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genome, wherein at least one of said genes has been disrupted by recombination with an internal fragment of that gene, the rest of said genes being operational to produce a spinosyn other than the one that would be produced if the disrupted gene were operational. Preferably the microorganism is an *S. spinosa* mutant.

The invention also provides a spinosyn-producing microorganism having operational spinosyn biosynthetic genes in its genome, wherein said genes a) include at least one operational PKS module more than or at least one less than is present in SEQ ID NO:1; or b) include a PKS module that differs from the corresponding module described in SEQ ID NO:1 by the deletion, inactivation, or addition of a KR, DH or ER domain, or by the substitution of an AT domain. Preferably the microorganism is an *S. spinosa* mutant.

The invention also provides spinosyns produced by cultivation of the novel microorganisms of the invention.

In another of its aspects the invention provides a process for isolating spinosyn biosynthetic genes which comprises creating a genomic library of a spinosyn producing microorganism, and using a labeled fragment of SEQ ID NO:1 that is at least 20 bases long as a hybridization probe.

Detailed Description of the Invention

A cosmid library of *S. spinosa* (NRRL 18395) DNA was constructed from fragments generated by partial digestion with *Sau*3A I. They were cloned into the *Bam*HI site of vector pOJ436 (See Fig. 3) (Bierman *et al.*, 1992) and introduced into *E. coli* cells by *in vitro* packaging and transduction. The library of recombinant bacteria thus prepared was screened for homology to two radiolabelled DNA probes by hybridization using the methods of Solenberg & Burgett (1989). One probe was the 400 kb *Spe*I fragment which is often deleted in non-producing *S. spinosa* strains generated by transformation or mutagenesis with N-methyl-N'-nitro-N-nitrosoguanidine (Matsushima *et al.*, 1994). The second probe was a 300 bp piece of *S. spinosa* DNA that codes for part of a ketosynthase not involved in spinosyn biosynthesis (B.E. Schoner, personal communication). It includes a region which is highly conserved in all polyketide and fatty acid synthase genes, and was therefore expected to cross-hybridize with the spinosyn PKS genes. Cosmids 9A6 and 2C10 were two of seven clones that hybridized to both probes. Cosmid 3E11 was selected

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from the genomic library by hybridization to a radiolabelled *Sgr*A1-*Bam*H1 fragment of cosmid 9A6 (bases 26757-26936 in SEQ ID NO: 1). To determine the nucleotide sequence of the insert in cosmid 9A6, *Bam*HI fragments were subcloned into the *Bam*HI site of plasmid pOJ260 (See Fig. 4) (Bierman *et al.*, 1992). The sequences of the inserts in these plasmids were determined by either of two methods. In one method, subcloned fragments were partially digested with *Sau*3A I, and size-selected pieces were cloned into the *Bam*HI site of DNA from the phage M13mp19. Single-stranded DNA was prepared from randomly selected recombinants, and sequenced by fluorescent cycle sequencing using reagents and equipment from ABI (Applied Biosystems, Inc., Foster, CA), according to the methods of Burgett & Rosteck (1994). The sequences from phage subclones of each plasmid were assembled into one contiguous sequence. In the other sequencing method, double-stranded plasmid DNAs were primed reiteratively with single-stranded oligonucleotides, each designed to complement a region near the end of previously determined sequence. The complete sequence was thus compiled from a series of partially-overlapping sequences. Prism-Ready Sequencing Kits (ABI) were used according to the manufacturer's instructions, and analyzed on an ABI373A Sequencer. The same strategy was employed to sequence across the *Bam*HI sites of double-stranded 9A6 DNA. These data allowed the subcloned sequences to be aligned and oriented relative to one another using the AssemblyLIGN module of the MacVector program (Oxford Molecular, Campbell, KY), and thereby allowed the entire nucleotide sequence of the *S. spinosa* DNA in cosmid 9A6 to be assembled. The complete sequences of cosmids 2C10 and 3E11 were determined by the method of fluorescent cycle sequencing of random DNA fragments cloned in phage M13 (SeqWright, Houston, TX). The inserts in cosmids 2C10 and 3E11 overlapped, and the insert in 3E11 overlapped the end of the insert in cosmid 9A6. See Fig. 2. Together, the three cosmid inserts spanned about 80 kb of unique sequence (SEQ ID NO: 1). The following Table 3 identifies the portions of SEQ ID NO:1 included in each of the three inserts.

Table 3

insert	bases in SEQ ID NO:1
cosmid 9A6	1-26941
cosmid 3E11	23489-57287
cosmid 2C10 (corrected)	41429-80161

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FIG. 2 gives a graphical representation of the relationship of the three inserts to the 80kb of sequence.

It should be noted that cosmid 2C10 was missing bases G41877, C45570, C57845 and G73173 of SEQ ID NO:1. These deletions were determined to be cloning artifacts. The deletions generated in-frame stop codons that truncated PKS polypeptides. One of them occurred in a region also cloned in cosmid 3E11, but was not present in the region of 3E11 for which sequence was obtained. Uncloned DNA spanning all 8 stop codons in the PKS region was therefore sequenced directly from PCR-amplified regions of the genome of *S. spinosa* (NRRL 18395). The sequences from uncloned DNA confirmed the existence of the 4 stop codons at the end of ACP domains, and proved that the 4 frameshifts within other coding regions were cloning artifacts unique to cosmid 2C10.

PKS Genes

SEQ ID NO:1 includes a central region of about 55 kb with striking homology to the DNA encoding the polyketide synthases of known macrolide producers (Donadio *et al.*, 1991; MacNeil *et al.*, 1992; Schwecke *et al.*, 1995; Dehoff *et al.*, 1997). The spinosyn PKS DNA region consists of 5 ORFs with in-frame stop codons at the end of ACP domains, similar to the PKS ORFs in the other macrolide-producing bacteria. The five spinosyn PKS genes are arranged head-to-tail (see FIG. 2), without any intervening non-PKS functions such as the insertion element found between the erythromycin PKS genes AI and AII (Donadio *et al.*, 1993). They are designated *spnA*, *spnB*, *spnC*, *spnD*, and *spnE*. The nucleotide sequence for each of the five spinosyn PKS genes, and the corresponding polypeptides, are identified in the following Table 4:

Table 4

GENE	BASES IN SEQ ID NO:1	CORRESPONDING POLYPEPTIDE
spnA	21111-28898	SEQ ID NO: 2
spnB	28916-35374	SEQ ID NO: 3
spnC	35419-44931	SEQ ID NO: 4
spnD	44966-59752	SEQ ID NO: 5
spnE	59803-76569	SEQ ID NO: 6

spnA encodes the initiator module (SEQ ID NO:1, bases 21126-24041) and extender module 1 (SEQ ID NO:1, bases 24102-28649). The nucleotide sequence and

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corresponding amino acid sequence for each of the functional domains within the initiator module and extender module 1 are identified in the following Table 5:

Table 5

spnA		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQ ID NO:2
KSi	21126-22379	6-423
ATi	22692-23669	528-853
ACPi	23793-24041	895-977
KS1	24102-25349	998-1413
AT1	25683-26684	1525-1858
KR1	27582-28121	2158-2337
ACP1	28404-28649	2432-2513

spnB encodes extender module 2 (SEQ ID NO:1, bases 29024-35125). The nucleotide sequence and corresponding amino acid sequence for each of the functional domains within extender module 2 are identified in the following Table 6:

Table 6

spnB		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQUENCE ID NO. 3
KS2	29024-30295	1-424
AT2	30629-31621	536-866
DH2	31697-32254	892-1077
ER2	33035-34072	1338-1683
KR2	34082-34621	1687-1866
ACP2	34886-35125	1955-2034

spnC encodes extender module 3 (SEQ ID NO:1, bases 35518-40035) and extender module 4 (SEQ ID NO:1, bases 40102-44676). The nucleotide sequence and corresponding amino acid sequence for each of the functional domains within extender modules 3 and 4 are identified in the following Table 7:

Table 7

spnC		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQ ID NO:4
KS3	35518-36786	1-423
AT3	37108-38097	531-280
KR3	38992-39528	1159-1337
ACP3	39790-40035	1425-1506
KS4	40102-41373	1529-1952
AT4	41713-42705	2066-2396
KR4	43615-44157	2700-2880
ACP4	44431-44676	2972-3053

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spnD encodes extender module 5 (SEQ ID NO:1, bases 45077-50254), extender module 6 (SEQ ID NO:1, bases 50318-54883), and extender module 7 (SEQ ID NO:1, bases 54947-59494). The nucleotide sequence and corresponding amino acid sequence for each of the functional domains within extender modules 5, 6, and 7 is identified in the following Table 8:

Table 8

spnD		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQ ID NO:5
KS5	45077-46348	1-424
AT5	46691-47674	539-866
DH5	47753-48310	893-1078
KR5	49226-49771	1384-1565
ACP5	50009-50254	1645-1726
KS6	50318-51592	1748-2172
AT6	51923-52915	2283-2613
KR6	53822-54361	2916-3095
ACP6	54638-54883	3188-3269
KS7	54947-56215	3291-3713
AT7	56549-57535	3825-4153
KR7	58106-58990	4344-4638
ACP7	59249-59494	4725-4806

spnE encodes extender module 8 (SEQ ID NO:1, bases 59902-65079), extender module 9 (SEQ ID NO:1, bases 65146-70401), and extender module 10 (SEQ ID NO:1, bases 70471-76566). The nucleotide sequence and corresponding amino acid sequence for each of the functional domains within extender modules 8, 9, and 10 is identified in the following Table 9:

Table 9

spnE		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQ ID NO:6
KS8	59902-61173	1-424
AT8	61489-62445	530-848
DH8	62548-63111	883-1070
KR8	64006-64557	1369-1552
ACP8	64843-65079	1648-1726
KS9	65146-66420	1749-2173
AT9	66760-67743	2287-2614
DH9	67819-68301	2640-2800
KR9	69370-69924	3157-3341
ACP9	70165-70401	3422-3500
KS10	70471-71745	3534-3948
AT10	72079-73071	4060-4390
DH10	73138-73692	4413-4597
KR10	74599-75135	4900-5078
ACP10	75415-75660	5172-5253

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spnE		
DOMAIN	BASES IN SEQ ID NO:1	AMINO ACIDS IN SEQ ID NO:6
TE10	75805-76566	5302-5555

The boundaries and functions of the 50 domains identified in the foregoing Tables 5-9 are predicted based on similarities to the conserved amino acid sequences of the domains in other polyketide synthases, particularly the erythromycin polyketide synthase (Donadio *et al.*, 1992). The unexpected KSi domain at the amino terminus of the initiator module is presumed to be non-functional because it contains a glutamine residue at amino acid 172, in place of the cysteine required for β-ketosynthase activity (Siggard-Andersen, 1993). A similar non-functional KS domain has been discovered in the initiator module of the tylosin PKS (Dehoff *et al.*, 1997). The other spinosyn PKS domains are functional. None of them has the sequence characteristics of the inactive domains found in the erythromycin and rapamycin PKS genes (Donadio *et al.*, 1991; Aparicio *et al.*, 1996). The cloned PKS genes were shown to be essential for spinosyn biosynthesis by the discovery that strains of *S. spinosa* in which these genes had been disrupted were unable to produce spinosyns by fermentation. Gene disruption was achieved by cloning an internal fragment of the gene into plasmid pOJ260 (Fig. 4), using procedures well-known to those skilled in the art. The recombinant plasmids were then introduced into *S. spinosa* by conjugation from *E. coli* using the procedures of Matsushima *et al.* (1994), and selecting for apramycin-resistant exconjugants. Plasmids based on pOJ260 do not replicate independently in *S. spinosa*, and are stably maintained by integrating the plasmid into the chromosome *via* recombination between the cloned DNA and its homologous sequence in the genome. Integration creates two incomplete versions of the targeted gene (one lacking 5' sequences and one lacking 3' sequences) in the chromosome, with the pOJ260 DNA between them. Spinosyn biosynthesis was blocked by disrupting the *spnA* ORF with the *Bam*H1 fragments V, N, or K, corresponding respectively to the following segments of SEQ ID NO: 1: 21365-22052, 22052-24338, or 24338-26227. Spinosyn biosynthesis was also blocked by disrupting the *spnD* ORF with *Bam*H1 fragments G, E, or K, corresponding respectively to the following segments of SEQ ID NO: 1: bases 48848-50578, 50578-52467, or 55207-55888. Spinosyn biosynthesis was also blocked by disrupting the

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spnE ORF with *Bam*H1 fragments J, I, D, H, and F, corresponding respectively to the following segments of SEQ ID NO: 1: 63219-63989, 65406-66733, 66733-68997, 69369-70731, and 70731-72675. Spinosyn biosynthesis was not blocked by integration *via Bam*H1 fragments C (bases 44612-47565 in SEQ ID NO: 1) or B (bases 55936-63219 in SEQ ID NO: 1) because they are not internal to any one gene; *Bam*H1 fragment C spans the junction between *spnC* and *spnD*, and *Bam*H1 fragment B spans the junction between *spnD* and *spnE*. In these cases, integration leaves one complete version of each gene.

Genes Adjacent to the PKS Responsible for Additional Modifications

In the DNA upstream of the PKS genes (cloned in cosmid 9A6) there were 16 open reading frames (ORFs), each consisting of at least 100 codons, beginning with ATG or GTG and ending with TAA, TAG or TGA, and having the codon bias expected of protein-coding regions in an organism whose DNA contains a high percentage of guanine and cytosine residues (Bibb *et al.*, 1984). See the bottom right hand side of FIG. 2 for a graphical representation of the 16 ORFs in 9A6. Based on evidence that will be discussed hereinafter, 14 of the ORFs have been designated as spinosyn biosynthetic genes, namely: *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, and *spnS* (they are labeled F through S in FIG. 2). In the following Table 10, the DNA sequence and the amino acid sequence for the corresponding polypeptide are identified for each of these genes, as well as for two ORFs (ORFL15 and ORFL16) found immediately upstream of *spnS*. Also identified in Table 10 are the nucleotide sequences for ORFR1 and ORFR2 downstream of the PKS genes (in cosmid 2C10), and the amino acid sequences corresponding to them.

Table 10

GENE	BASES IN SEQUENCE ID NO: 1	POLYPEPTIDE
spnF	20168-20995	SEQ ID NO: 7
spnG	18541-19713 (C)	SEQ ID NO: 8
spnH	17749-18501 (C)	SEQ ID NO: 9
spnI	16556-17743	SEQ ID NO: 10
spnJ	14799-16418 (C)	SEQ ID NO: 11
spnK	13592-14785 (C)	SEQ ID NO: 12
spnL	12696-13547 (C)	SEQ ID NO: 13
spnM	11530-12492 (C)	SEQ ID NO: 14
spnN	10436-11434	SEQ ID NO: 15
spnO	8967-10427	SEQ ID NO: 16
spnP	7083-8450	SEQ ID NO: 17
spnQ	5363-6751 (C)	SEQ ID NO: 18

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GENE	BASES IN SEQUENCE ID NO: 1	POLYPEPTIDE
spnR	4168-5325 (C)	SEQ ID NO: 19
spnS	3416-4165 (C)	SEQ ID NO: 20
ORFL 15	2024-2791	SEQ ID NO: 21
ORFL 16	1135-1971 (C)	SEQ ID NO: 22
ORFR 1	76932-77528	SEQ ID NO: 23
ORFR 2	77729-79984	SEQ ID NO: 24

(C) indicates complementary strand is given in the sequence listing

To assign functions to the polypeptides identified in Table 10, three lines of evidence were utilized: similarity to sequences of known function, results of targeted gene disruption experiments, and results of bioconversion experiments.

The amino acid sequences of the predicted polypeptides were compared to sequences deposited in the databases at the National Center for Biotechnology Information (NCBI, Washington, DC), using the BLAST algorithm to determine how well they are related to known proteins. The BLAST searches of the NCBI databases were also repeated periodically to obtain new insights from additional homologies. Table 11 gives the best matches from a basic BLAST search on January 12, 1998:

Table 11

Gene	Significant Protein Match	GenBank Accession	BLAST Score*	Reported function
spnF	C-24 sterol methyltransferase (*Zea mays*)	U79669	202	C-methylation
spnG	Daunosamyl transferase *dnrS* (*Streptomyces peucetius*)	L47164	202	sugar addition
spnH	Mycinamicin III O-methyltransferase (*Micromonospora griseorubida*)	D16097	408	sugar methylation
spnI	*ORFY* (*Streptomyces nogalater*)	Z48262	192	unknown
spnJ	Hexose oxidase (*Chondrus crispus*)	U89770	143	oxido-reduction
spnK	*ORFY* (*Streptomyces nogalater*)	Z48262	137	unknown
spnL	C-24 sterol methyltransferase (*Zea mays*)	U79669	166	C-methylation
spnM	Unknown (*Mycobacterium tuberculosis*)	Z95586	132	unknown
spnN	*RdmF* (*Streptomyces purpurascens*)	U10405	409	unknown
spnO	2,3 dehydratase *EryB*V1 (*Saccharopolyspora erythraea*)	Y11199	595	deoxysugar synthesis
spnP	Mycarosyl transferase *EryB*V (*Saccharopolyspora erythraea*)	U77459	336	sugar addition
spnQ	CDP-4-keto-6-deoxy-D-glucose-3-dehydrase (*Salmonella enterica*)	P26398	784	dideoxysugar synthesis
spnR	Spore coat polysaccharide biosynthesis protein (*Bacillus subtilis*)	P39623	286	sugar transamination
spnS	TDP-N-dimethyldesosamine-N-methyltransferase *EryC*VI (*Saccharopolyspora erythraea*)	U77459	484	aminosugar methylation
ORFL15	Keto acyl reductase (*Streptomyces cinnamonensis*)	Z11511	132	oxido-reduction

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Gene	Significant Protein Match	GenBank Accession	BLAST Score*	Reported function
ORFL16	Regulatory protein of the *als* operon, (*Bacillus subtilis*)			transcription control
ORFR1	None			
ORFR2	Conjugation transfer protein (*Bacillus subtilis*)	Z99117	328	DNA replication

* Greater similarity is associated with higher BLAST scores (Altschul *et al.*, 1990).

In targeted gene disruptions, internal fragments were generated by PCR amplification from the cosmid DNAs, and cloned into plasmid pOJ260. The resulting plasmids were then conjugated into *S. spinosa* (NRRL 18395), and apramycin-resistant exconjugants were isolated and fermented. As stated earlier, the basis of disruption experiments is that when a plasmid bearing an internal gene fragment is integrated, two incomplete copies of the biosynthetic gene result, thereby eliminating the enzymatic function. Resulting fermentation products were analyzed to determine which spinosyns accumulated. The results of the targeted gene disruption experiments are summarized in Table 12.

In bioconversion studies, strains in which spinosyn synthesis was altered were tested for their ability to convert available spinosyn intermediates to other spinosyns. The intermediates used were spinosyn A Aglycone (AGL), spinosyn P (P), spinosyn K (K), and spinosyn A 9-Psa (PSA). The results of the bioconversion experiments are also summarized in Table 12

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Table 12

Disrupted Gene	Internal Fragment in SEQ ID NO: 1	spinosyns accumulated	Bioconversion products AGL→	P→	K→	PSA→
None	None	A+D				
spnF	20325-20924	None	A	A		A
spnG	18818-19426	None	AGL	K		A
spnG-H	18511-19559	P			K	A
spnI	16699-17400	None		J	A	A
spnJ	14866-15470	None	A		A	
spnK	13785-14574	None				
spnL	12791-13428	None	A	A		A
spnM	11705-12371	3% A	A			A
spnN	10636-11369	PSA				
spnO	9262-10226	PSA				
spnP	7391-8159	PSA	PSA			
ORFL15	2145-2719	A+D				
ORFL16	1226-1852	A+D				
ORFR2	79321-79855	A+D				

The conclusions drawn from BLAST searches, the gene disruption experiments, and the bioconversion studies will now be discussed in greater detail on a gene by gene basis.

The 11 genes upstream of the PKS were shown to be involved in spinosyn biosynthesis because strains in which they were disrupted failed to accumulate the major spinosyns A and D (Table 12). The next 2 genes upstream (ORFL15, ORFL16), and the large gene downstream (ORFR2) of the PKS, do not contribute to spinosyn production because fermentation was not affected by their disruption (Table 12). Disruption of the ORF immediately downstream of the PKS genes (ORFR1) was not attempted because it was too small to yield an internal fragment that would recombine at an acceptable frequency. Disruptions of the *spnQ, spnR,* and *spnS* genes were not attempted because early BLAST searches showed that these genes had striking similarity to enzymes known to be involved in the biosynthesis of unusual deoxysugars. *spnQ* had 53% identity between its gene product and the CDP-4-keto-6-deoxy-D-glucose-3-dehydrase involved in synthesis of the abequose moiety of the *Salmonella enterica* cell surface lipopolysaccharide (Jiang *et al.*, 1991); *spnR* had up to 40% identity between its product and a group of proteins proposed to function as deoxysugar transaminases (Thorson *et al.*, 1993); and *spnS* had 42% identity between its product and the *SrmX* product of *Streptomyces ambofaciens*, an organism that synthesizes the forosamine-containing antibiotic spiramycin (Geistlich *et al.*, 1992). Even stronger similarities have emerged from recent BLAST searches (Table 11).

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Based on these similarities, and the close linkage of the genes to other spinosyn biosynthetic genes, it is concluded that *spnQ, spnR,* and *spnS* are involved in production of the forosamine moiety of spinosyns.

spnF, spnJ, spnL, spnM

Strains disrupted in genes *spnF, spnJ, spnL* or *spnM* did not accumulate any spinosyns to significant levels (the low level of spinosyn A in the *spnM* mutant presumably resulted from some residual activity in the gene product deleted at its carboxy terminus). However, they bioconverted exogenously-supplied aglycone to spinosyn A, and therefore contained all the enzymes necessary for the later steps in spinosyn biosynthesis. These particular genes must be involved in generation of the aglycone from the putative monocyclic lactone product of the PKS genes. Roles for *spnF* and *spnL* in the formation of carbon-carbon bridges are consistent with their similarities to enzymes that methylate carbon atoms (Table 11). The absence of partially modified intermediates in the blocked mutants may result from instability of the compounds, or from reduced biosynthesis due to lack of glycosylated molecules to act as positive regulators, analogous to those of the tylosin pathway (Fish & Cundliffe, 1997).

spnG, spnH, spnI, spnK

Disruption of *spnG* also prevented spinosyn production, but the mutant strain could not bioconvert aglycone so this gene is required for a later step in the pathway (Table 12). Its sequence similarity to known glycosyl transferase genes (Table 11) suggests that *spnG* encodes the rhamnosyl transferase required for addition of the first sugar to the aglycone. The mutant with a disrupted *spnG* also lacked a functional 4'-O-methyltransferase (OMT) because it converted the 3',4'-didesmethyl spinosyn (P) to the 4'-desmethyl spinosyn (K), but not to the fully methylated spinosyn A. The 4'-OMT activity was presumably not expressed in the mutant because the encoding gene (*spnH*) lies downstream of the disrupting integration in the same operon. The existence of this operon was confirmed by disrupting *Bam*H1 fragment T, which spans the junction between *spnG* and *spnH* but is not internal to any open reading frame. Nevertheless, its disruption altered spinosyn synthesis, so this fragment must be internal to a single transcript that encompasses both genes. In addition to the expected loss of 4'-OMT activity encoded by *spnH*, this disruption also caused the

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unexpected loss of 3'-OMT function, leading to accumulation of spinosyn P (Table 12). The 3'OMT activity appears to be encoded by the convergent downstream gene, *spnI*. This gene has most sequence similarity to the ORF Y gene of *Streptomyces nogalator* (Table 11). The function of the ORF Y product is unknown, but the organism produces an unusual tetra-methylated deoxysugar (nogalose) that is similar to the tri-methylated rhamnose of spinosyn A, so presumably both genes are involved in sugar methylation. Consistent with this hypothesis, disruption of *spnI* created a mutant that bioconverted spinosyn P only to the 3'-desmethyl spinosyn (J), not spinosyn A (Table 12). The disruption prevented any spinosyn accumulation in unsupplemented fermentations. *spnK* has a sequence similar to *spnI* and ORF Y, and presumably encodes the 2'-OMT. Its disruption also prevented accumulation of any spinosyns in unsupplemented fermentations (Table 12).

spnN, spnO, spnP

Disruption of genes *spnN*, *spnO* and *spnP* led to accumulation of the pseudoaglycone (Table 12). These genes are therefore involved in the biosynthesis or addition of the forosamine sugar. The similarity of *spnP* to glycosyl transferases (Table 11) indicates that it encodes the spinosyn forosamyl transferase. The high degree of similarity between *spnO* and a 2,3 dehydratase (Table 11) indicates that it is involved in the 2'-deoxygenation step of forosamine synthesis.

Rhamnose Genes

The overlapping inserts cloned in cosmids 9A6, 3E11 and 2C10 do not contain genes that encode the four enzymes required to produce rhamnose from glucose (Liu & Thorson, 1994). The first enzyme is a glucose thymidylate transferase (*gtt*), or equivalent enzyme, that activates glucose by addition of a nucleotidyl diphosphate (NDP). The second is a glucose dehydratase (*gdh*) to produce NDP-4-keto-6-deoxy-glucose, an intermediate common to many deoxysugar biosynthetic pathways. An epimerase (*epi*) and a ketoreductase (*kre*) specific for rhamnose synthesis are also required, to convert the NDP-4-keto-6-deoxy-glucose to NDP-L-rhamnose, the activated sugar that is the substrate of the glycosyltransferase adding rhamnose to the aglycone. Genes that code for these enzymes in *S. spinosa* were cloned from a separate library of 7-12 kb partial *Sau*3A I fragments in the λ vector ZAP Express™ (Stratagene, LaJolla, CA). Radiolabelled probes were prepared by random primer

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extension (Boehringer Mannheim, Indianapolis, IN) of fragments from plasmid pESC1 containing the *Saccharopolyspora erythraea gdh* (Linton *et al.*, 1995) and *gtt* genes. Plaque hybridizations to screen the phage library were performed with a stringent wash of 0.5x SSC, 0.1%SDS at 65°C for 1h. The plasmid (pDAB1620 and pDAB1621) portions of the vector containing inserts were excised from two of the three hybridizing phage, and partially sequenced using Prism-Ready Sequencing Kits (ABI) and multiple primers. The sequenced part of the insert in pDAB1620 (SEQ ID NO: 25) includes an ORF that would encode a 329-amino acid polypeptide (SEQ ID NO:26) with 82% identity to the *gdh* product of S. *erythraea*. Adjacent to this gene is an ORF coding for a 275-amino acid polypeptide (SEQ ID NO:27) with 72% identity to the *S. erythraea kre* gene product. The sequenced part of the insert in pDAB1621 (SEQ ID NO: 28) contains an ORF encoding a 261-amino acid polypeptide (SEQ ID NO: 29) with 83% identity to the *S. erythraea gtt* gene product. A second probe for rhamnose genes was prepared by PCR amplification of *S. spinosa* genomic DNA using degenerate oligonucleotide primers (SEQ ID NO: 30 and SEQ ID NO: 31) based on conserved amino acid regions in known *epi* proteins (Jiang *et al.*, 1991; Linton *et al.*, 1995). PCR reactions were performed in a GeneAmp 9600 Thermocycler with AmpliTaq polymerase (Perkin-Elmer) using 30 cycles of 30 sec at 94°C, 30 sec at 60°C and 45 sec at 72°C. The probe hybridized to one phage in the 7-12 kb library; the plasmid portion of the vector containing this insert (pDAB1622) was excised and partially sequenced (SEQ ID NO:32). It includes an ORF for a 202-amino acid polypeptide (SEQ ID NO:33) with 57% homology to the *S. erythraea epi* protein. The genes were disrupted by recombination with plasmids containing internal fragments (bases 382-941 in SEQ ID NO: 25, 1268-1867 in SEQ ID NO:25, 447-994 in SEQ ID NO:28 or 346-739 in SEQ ID NO:32). Apramycin-resistant exconjugants were obtained in all cases, but they were only capable of growth on osmotically-stabilized media such as CSM supplemented with sucrose at 200 g/L, or R6 (Matsushima *et al.*, 1994). Even under these conditions, they grew much slower than the parent *S. spinosa* (NRRL 18395), and were morphologically distinct, with highly fragmented mycelia. These results could be due to the presence of rhamnose in the cell wall in *S. spinosa* and a requirement that these four genes be present for normal cell wall synthesis in this organism. Mutants disrupted in these genes grew too slowly

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to be fermented under conditions known to produce spinosyns. However, Southern hybridizations of *S. spinosa* genomic DNA with the *S. erythraea gtt/gdh* probe (washed in 2x SSC, 0.1%SDS at 65°C for 1h) or with the degenerate *epi* probe (washed in 0.1x SSC, 0.1%SDS at 65°C for 1h) indicated that there are no other homologues of these genes present in the *S. spinosa* genome. Therefore, the four cloned *S. spinosa* genes must be the sole source of rhamnose for both cell wall formation and spinosyn biosynthesis.

The nucleotide sequence and corresponding amino acid sequence for each of the four *S. spinosa* genes required to produce rhamnose are identified in the following Table 13:

Table 13

gene	DNA sequence	amino acid sequence
S. spinosa gtt	SEQ ID NO:28, bases 334-1119	SEQ ID NO:29
S. spinosa gdh	SEQ ID NO:25, bases 88-1077	SEQ ID NO:26
S. spinosa epi	SEQ ID NO:32, bases 226-834	SEQ ID NO:33
S. spinosa kre	SEQ ID NO:25, bases 1165-1992	SEQ ID NO:27

Thus 23 genes from *S. spinosa* can be assigned roles in spinosyn biosynthesis: 5 PKS genes to produce a macrocyclic lactone, 4 genes to modify this to the aglycone, 5 genes to synthesize and add rhamnose, 3 genes to methylate the rhamnose, and 6 genes to synthesize and add forosamine. The hypothetical biosynthetic pathway is summarized in Fig 1.

Utility

There are many uses for the cloned *Saccharopolyspora spinosa* DNA. The cloned genes can be used to improve yields of spinosyns and to produce new spinosyns. Improved yields can be obtained by integrating into the genome of a particular strain a duplicate copy of the gene for whatever enzyme is rate limiting in that strain. In the extreme case where the biosynthetic pathway is blocked in a particular mutant strain due to lack of a required enzyme, production of the desired spinosyns can be restored by integrating a copy of the required gene. Yield

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improvement obtained by integrating copies of spinosyn genes is illustrated hereinafter in Examples 1-3 and 6.

Novel spinosyns can be produced using fragments of the cloned DNA to disrupt steps in the biosynthesis of spinosyns. Such disruption may lead to the accumulation of precursors or "shunt" products (the naturally-processed derivatives of precursors). The fragments useful in carrying out disruptions are those internal to a gene with bases omitted from both the 5' and 3' ends of the gene. Homologous recombination events utilizing such fragments result in two partial copies of the gene: one that is missing the omitted bases from the 5' end and one that is missing the omitted bases from the 3' end. The number of bases omitted at each end of the fragment must be large enough so that neither of the partial copies of the gene retains activity. At least 50 bases will normally be omitted from each end, and more preferably at least 100 bases are omitted from each end. The length of the partial gene fragment should be large enough so that recombination frequency is high enough for a practical experiment. Useful fragments for disruptions are desirably at least 300 bases long, and more preferably at least about 600 bases long. Modified spinosyns produced by disrupting genes may be insect control agents themselves, or serve as substrates for further chemical modification, creating new semi-synthetic spinosyns with unique properties and spectra of activity. Example 4 hereinafter illustrates the use of disruption.

Novel spinosyns can also be produced by mutagenesis of the cloned genes, and substitution of the mutated genes for their unmutated counterparts in a spinosyn-producing organism. Mutagenesis may involve, for example: 1) deletion or inactivation of a KR, DH or ER domain so that one or more of these functions is blocked and the strain produces a spinosyn having a lactone nucleus with a double bond, a hydroxyl group, or a keto group that is not present in the nucleus of spinosyn A (*see* Donadio *et al.*, 1993); 2) replacement of an AT domain so that a different carboxylic acid is incorporated in the lactone nucleus (*see* Ruan *et al.*, 1997); 3) addition of a KR, DH, or ER domain to an existing PKS module so that the strain produces a spinosyn having a lactone nucleus with a saturated bond, hydroxyl group, or double bond that is not present in the nucleus of spinosyn A; or 4) addition or subtraction of a complete PKS module so that the cyclic lactone nucleus has a greater

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or lesser number of carbon atoms. Example 5 illustrates use of mutagenesis to produce a spinosyn with modified functionality.

The DNA from the spinosyn gene cluster region can be used as a hybridization probe to identify homologous sequences. Thus, the DNA cloned here could be used to locate additional plasmids from the *Saccharopolyspora spinosa* gene libraries which overlap the region described here but also contain previously uncloned DNA from adjacent regions in the genome of *Saccharopolyspora spinosa*. In addition, DNA from the region cloned here may be used to identify non-identical but similar sequences in other organisms. Hybridization probes are normally at least about 20 bases long and are labeled to permit detection.

The modified strains provided by the invention may be cultivated to provide spinosyns using conventional protocols such as those disclosed in U. S. Patent No. 5,362,634.

The following examples are provided in order that the invention might be more completely understood. They should not be construed as limitations of the invention.

Example 1

Improved yield of spinosyns A and D by transformation with Cosmid 9A6

Vegetative cultures of *S. spinosa* strain NRRL18538 were grown in 50 ml CSM medium (trypticase soy broth 30 g/l, yeast extract 3 g/l, magnesium sulfate 2 g/l, glucose 5 g/l, maltose 4 g/l) in 250 ml Erlenmeyer flasks shaken at 300 rpm at 30°C for 48h. Fermentation cultures contained a 1 ml inoculum of this vegetative culture in 7 ml of INF202, a proprietary medium similar to that described in Strobel & Nakatsukasa (1993). The cultures were grown in 30 ml plastic bottles arranged in 10x10 modules, shaken at 300 rpm in a 30°C room for 3, 5 or 7 days. Broths were extracted with 4 volumes of acetonitrile, then analyzed for spinosyns A+D by isocratic high pressure liquid chromatography (HPLC) through a C-18 reversed-phase column (Strobel and Nakatsukasa, 1993). The amount of spinosyns was determined from absorbance at 250 nm. For each time point, spinosyns A + D were determined from 10 fermentation bottles. Two representative samples from each set of replicates were also analyzed by a slightly modified HPLC system for pseudoaglycone (PSA),

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the spinosyn precursor which lacks forosamine. In this system the mobile phase is 35:35:30 acetonitrile/methanol/0.5% (w/v) aqueous ammonium acetate (R. Wijayaratne, unpublished).

The cultures contain not only the insect-active spinosyns A and D, but also pseudoaglycone (Table 14).

Table 14

Spinosyn production in strain NRRL 18538

Time	A+D (μg/ml)	PSA (μg/ml)
3d	101 ± 3	109 ± 11
5d	269 ± 14	155 ± 26
7d	334 ± 32	110 ± 53

The values are means ± 95% confidence levels.

The accumulation of the pseudoaglycone, a forosamine-deficient precursor of spinosyn A, suggests that, in this strain grown under these conditions, the yield of spinosyns A + D is limited by the supply and/or addition of forosamine

Cosmid 9A6 was conjugated from *E. coli* strain S17-1 (Simon *et al.*, 1983) into *S. spinosa* strain NRRL 18538 using the method of Matsushima *et al.* (1994). Six independent isolates transformed with Cosmid 9A6 were subsequently grown and analyzed for spinosyn factor production under the fermentation conditions described above. The average yield of spinosyns A + D from these strains was higher than from their parent, by 35 μg/ml after 3 days of fermentation, and by 37 μg/ml after 5 days. The amount of pseudoaglycone in the transformed cultures was lower than in the parent strain throughout the fermentation (Table 15)

Table 15

Spinosyn production in derivatives of NRRL 18538 transformed with Cosmid 9A6.

Time	A+D (μg/ml)	PSA (μg/ml)
3d	136 ± 4	31 ± 2
5d	306 ± 5	7 ± 2
7d	365 ± 7	7 ± 1

The values are means ± 95% confidence levels.

Strain NRRL 18538 and 6 independent isolates transformed with Cosmid 9A6 were analyzed for spinosyn content at different times during fermentation. For each strain, spinosyns A+D were determined from 10 fermentation bottles (Table 16). Two samples from each set of replicates were also analyzed for pseudoaglycone content (Table 17).

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Table 16

Effect of Cosmid 9A6 on spinosyn A+D in NRRL 18538

Time	- 9A6	+ 9A6	Effect of 9A6
3d	101 ± 3	136 ± 4	+35%
5d	269 ± 14	306 ± 5	+14%
7d	334 ± 32	365 ± 7	+9%
9d	414 ± 17	411 ± 8	-1%

The values are means in μg/ml ± 95% confidence levels.

Table 17

Effect of Cosmid 9A6 on pseudoaglycone accumulation in NRRL 18538

Time	- 9A6	+ 9A6	Effect of 9A6
3d	109 ± 11	31 ± 2	-72%
5d	155 ± 26	7 ± 2	-95%
7d	110 ± 53	7 ± 1	-94%
9d	119 ± 11	5 ± 1	-96%

The values are means in μg/ml ± 95% confidence levels.

It has therefore been demonstrated that transformation with Cosmid 9A6 can improve the efficiency with which precursor pseudoaglycone is processed to spinosyns. In NRRL 18538, the yield improvements for spinosyn A+D were 35% after 3 days of fermentation, and 14% after 5 days (Table 15). The rate-limiting process appears be the supply and/or addition of forosamine because pseudoaglycone was present in the parent at about 120 μg/ml throughout the fermentation, but in the transconjugants it was reduced to about 30 μg/ml at 3 days, and essentially depleted thereafter (Table 15). Although the conversion was not quantitative, the data are consistent with an improved efficiency in the processing of pseudoaglycone to spinosyn A+D in strains transformed with Cosmid 9A6. The effect could be the result of duplicating a forosamine biosynthetic gene, a forosaminyltransferase gene, or a combination of improvements. There was no statistically significant difference between the spinosyn A+D yields from the NRRL 18358 strains with or without Cosmid 9A6 after 7 or 9 days fermentation. Pseudoaglycone was still reduced in the transconjugants, but the extra spinosyn A+D produced by its conversion may not have been detectable against the higher background of spinosyns accumulated by this stage of the fermentation.

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Example 2

Correction of methylation deficiencies in strain NRRL 18823 by Cosmid 9A6

Although spinosyn synthesis is limited by forosamine supply/addition in strain NRRL 18358, other biosynthetic functions may be limiting in other strains. *S. spinosa* strain NRRL18823 accumulates spinosyn H (2'-desmethyl-spinosyn A; Kirst *et al.*, 1992), rather than spinosyn A. Spinosyn H is not an intermediate in the spinosyn A biosynthetic pathway, but a "shunt" product synthesized naturally when 2'-O-methylation does not occur. Cosmid 9A6 was conjugated from *E. coli* strain S17-1 into strain NRRL 18823 using the method described above. Two of the resulting exconjugants, when fermented, produced predominantly spinosyn A, with little spinosyn H (Table 18).

Table 18

Strain	H (µg/ml)	A+D (µg/ml)
NRRL 18823	323	0
NRRL 18823/9A6-2	36	551
NRRL 18823/9A6-5	45	646

This shows that transformation with Cosmid 9A6 is able to overcome a second type of limitation to spinosyn production - the methylation deficiency in strain NRRL 18823.

Example 3

Correction of 4'-O-methylation deficiency in strain NRRL 18743 by Cosmid 9A6

S. spinosa strain NRRL18743 accumulates spinosyn K (4'-desmethyl-spinosyn A), an intermediate in the spinosyn A biosynthetic pathway. Two of the exconjugants of strain NRRL 18743 containing Cosmid 9A6 produced predominantly spinosyn A, with little spinosyn K, while the third produced no detectable spinosyn K (Table 19).

Table 19

Strain	K (µg/ml)	A+D (µg/ml)
NRRL 18743	488	0
NRRL 18743/9A6-1	38	829
NRRL 18743/9A6-2	22	725
NRRL 18743/9A6-3	0	706

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This demonstrates that transformation with Cosmid 9A6 is able to overcome a third type of limitation to spinosyn A production - the methylation deficiency in strain NRRL 18743.

Example 4

Accumulation of spinosyn precursor caused by disruption of *spnP*

An internal fragment of *spnP* (bases 7391 - 8159) was amplified in a polymerase chain reaction using primers given in SEQ ID NO:34 and SEQ ID NO:35. AmpliTaq polymerase (Perkin Elmer, Foster City, CA) was used according to the manufacturer's instructions, in a 100 µl reaction with 20 pmoles of each primer and 1 µg of 9A6 DNA. The mixture was subjected to 25 cycles of 60 sec at 94°C, 60 sec at 37°C and 120 sec at 72°C. The amplification product was cloned as an *Eco*R1-*Hin*dIII fragment into the plasmid vector pOJ260 (Bierman *et al.*, 1992), then conjugated from *E. coli* S17-1 into *S. spinosa* NRRL 18538. Stable exconjugants, resulting from a single homologous recombination event between the plasmid-born and chromosomal sequences, contain a copy of the vector DNA integrated into the chromosome between two incomplete copies of *spnP*. When fermented, these exconjugants accumulate the forosamine-deficient precursor pseudoaglycones, rather than the end products spinosyns A and D (Table 20).

Table 20

Strain	PSA (µg/ml)	A+D (µg/ml)
NRRL 18538	79	284
NRRL 18538/1614-2	416	22
NRRL 18538/1615-1	372	21
NRRL 18538/1615-2	543	21
NRRL 18538/1615-5	476	19
NRRL 18538/1615-6	504	18

The pseudoaglycones are intermediates useful in the preparation of known insecticides (International Application WO 93/09126)

Example 5

Accumulation of a novel spinosyn following modification of the PKS domain ER2

Overlapping, complementary oligonucleotides SEQ ID NO: 36 and SEQ ID NO: 37 were designed to modify the gene encoding the enoyl reductase function in module 2 of the spinosyn PKS. These mutagenic primers provide for substitution of

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the sequence TCACC in place of GGTGG at bases 33563-33567 of SEQ ID NO:1, so that the sequence encodes a serine-proline dipeptide instead of a glycine-glycine dipeptide in the putative NAD(P)H-binding motif. A similar substitution was successfully used to inactivate an erythromycin ER without affecting any other PKS functions (Donadio *et al.*, 1993). The substitution simultaneously introduced a novel *Pin*A1 restriction site, and eliminated a *Sgr*A1 site, to facilitate detection of the engineered DNA in recombinant organisms.

In the first step of the mutagenesis, two separate PCR amplifications were performed, one using the mutagenic primer SEQ ID NO: 36 and flanking primer SEQ ID NO: 38, the other using mutagenic primer SEQ ID NO: 37 and flanking primer SEQ ID NO: 39. In the second step, the products of the first reactions were diluted 100-fold, pooled and amplified with only the flanking primers SEQ ID NO: 38 and SEQ ID NO: 39. In the third step, the products of the second PCR reaction were cloned into the plasmid pCRII according to the manufacturer's instructions (InVitrogen, San Diego, CA). A portion of the mutated ER2 domain (spanning bases 33424-33626 in SEQ ID NO: 1) was excised as a *Van*911-*Nhe*I fragment, and inserted in place of the wild-type *Van*911-*Nhe*I fragment in a 3.5 kb *Eco*R1 fragment of cosmid 3E11 (bases 32162-35620 in SEQ ID NO: 1) cloned in the plasmid pBluescript SK- (Stratagene). The mutated *Eco*R1 fragment was then transferred into the conjugative plasmid pDAB1523 (FIG 5), a derivative of pOJ260 containing the *rpsL* gene of *Streptomyces roseosporus* that confers a counter-selectable streptomycin-sensitive phenotype (Hosted & Baltz, 1997). The resultant plasmid containing the mutated *Eco*R1 fragment was conjugated from *E. coli* S17-1 (Simon *et al.*, 1983) into SS15, a spontaneous streptomycin-resistant derivative of *S. spinosa* strain NRRL18538, using the method of Matsushima *et al.* (1994). (Spontaneous streptomycin-resistant derivatives of *S. spinosa* strain NRRL18538 can be readily isolated by those skilled in the art.) Apramycin-resistant exconjugants were shown to contain both wild-type and mutated versions of the ER2 domain by Southern hybridization with digoxygenin-labeled probes (Boehringer Mannheim). They also contained the *S. roseosporus rpsL* gene and consequently, on BHI agar (Difco, Detroit, MI) containing streptomycin at 150 mg/L, they grew poorly and failed to produce aerial mycelium. Spontaneous revertants to streptomycin-resistance were

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selected on the basis of their ability to grow and produce white, aerial mycelium on BHI agar containing streptomycin at 150 mg/L. Southern analysis indicated that these strains no longer contained the *S. roseosporus rpsL* gene or any other pDAB1523 sequences. Some strains had lost the entire cluster of spinosyn biosynthetic genes, including the ER2 domain, as well as pDAB1523. In other strains the pDAB1523 sequences had been excised along with the mutant ER2 domain, re-creating the parental gene structure. In a third type of streptomycin-resistant strain, the pDAB1523 had been excised with the wild-type ER2 domain, leaving the mutated version in its place. When fermented, a strain of this third type produced a novel metabolite, separable from spinosyn A by liquid chromatography on a C18 column (ODS-AQ, YMC, Wilmington, NC) using a mobile phase of acetonitrile: methanol: 2% ammonium acetate (44:44:12). The new entity was analyzed by electrospray ionization and tandem mass spectroscopy (Balcer *et al.*, 1996) using a triple quadrupole mass spectrometer (TSQ700, Finnigan MAT, San Jose, CA). It had the properties expected of the C18:C19-anhydrospinosyn A, with a mass of 729.5 daltons and produced the 142 dalton forosamine fragment. We conclude that modification of DNA encoding PKS domains results in the production of novel fermentation products.

Example 6

Improved yield of spinosyns A and D by transformation of NRRL 18538 with rhamnose biosynthetic genes

Fragments containing the rhamnose biosynthetic genes were cloned independently into the conjugative vector pOJ260 (Bierman *et al.*, 1992). The resulting plasmids are listed in Table 21.

Table 21

Plasmid	Genes
pDAB1632	*gtt*
pDAB1634	*gdh+kre*
pDAB1633	*epi*

Each plasmid was conjugated from *E. coli* S17-1 (Simon *et al.*, 1983) into *S. spinosa* NRRL 18538 by the method of Matsushima *et al.* (1994). Apramycin-resistant exconjugants, presumably containing a plasmid integrated into the chromosome by homologous recombination, were selected and fermented (Table 22).

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Table 22

Spinosyn production in derivatives of NRRL 15328 transformed with rhamnose genes

Strain	Duplicated Genes	A+D (μg/ml)	
		Experiment 1	Experiment 2
NRRL 18538	None	344 ± 39	405 ± 25
NRRL 18538/1632-1	*gtt*	410 ± 21	418 ± 38
NRRL 18538/1634-1	*gdh+kre*	351 ± 27	360 ± 21
NRRL 18538/1633-1	*epi*	318 ± 29	315 ± 18

The values are means ± 95% confidence limits.

In derivatives of NRRL 15328 transformed with *gtt* or *epi*, or the combination of *gdh* and *kre*, there was no consistent increase in the yield of spinosyns.

The fragments containing the *gtt* and *gdh+kre* genes were combined in a single plasmid. Two plasmids containing the combined *gtt*, *gdh* and *kre* genes (pDAB1654 and pDAB1655) were isolated, and conjugated from *E. coli* S17-1 (Simon *et al.*, 1983) into *S. spinosa* NRRL 18538 by the method of Matsushima *et al.* (1994). Apramycin-resistant exconjugants were selected and fermented (Table 23).

Table 23

Spinosyn production in derivatives of NRRL 15328 transformed with rhamnose genes

Strain	Duplicated Genes	A+D (μg/ml)	
		Experiment 1	Experiment 2
NRRL 18538	None	109±9	133±36
NRRL 18538/1654-2	*gtt*, *gdh* and *kre*	323±19	244±34
NRRL 18538/1654-5	*gtt*, *gdh* and *kre*	571±23	412±61
NRRL 18538/1654-6	*gtt*, *gdh* and *kre*	577±17	425±51
NRRL 18538/1654-11	*gtt*, *gdh* and *kre*	587±23	426±55
NRRL 18538/1655-1	*gtt*, *gdh* and *kre*	501±20	395±59
NRRL 18538/1655-3	*gtt*, *gdh* and *kre*	537±27	421±63
NRRL 18538/1655-5	*gtt*, *gdh* and *kre*	529±21	428±47
NRRL 18538/1655-12	*gtt*, *gdh* and *kre*	526±26	401±60

The values are means ± 95% confidence limits.

In derivatives of NRRL 15328 transformed with the *gtt*, *gdh* and *kre* genes, significant increases in spinosyn yields were observed. This probably results from overcoming a rate-limiting supply of NDP-4-keto-6-deoxy-glucose by simultaneously increasing the amounts of both *gtt* and *gdh* gene products, the enzymes necessary for its biosynthesis (see Fig. 1). A greater supply of the NDP-4-keto-6-deoxy-glucose intermediate would lead to increased production of both rhamnose and forosamine,

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and therefore greater ability to convert aglycone to spinosyns A+D. Consistent with the hypothesis that deoxysugar supply is limiting spinosyn production in NRRL 18538, many mutants blocked in forosamine synthesis or addition accumulate PSA to very high levels. More of this intermediate can be made because it requires only one deoxysugar, compared with the two required for spinosyns A or D.

The present invention is not limited to a particular vector comprising spinosyn genes of the invention, but rather encompasses the biosynthetic genes in whatever vector is used to introduce the genes into a recombinant host cell.

In addition, due to the degeneracy of the genetic code, those skilled in the art are familiar with synthetic methods of preparing DNA sequences which may code for the same or functionally the same activity as that of the natural gene sequence. Likewise, those skilled in the art are familiar with techniques for modifying or mutating the gene sequence to prepare new sequences which encode the same or substantially the same polypeptide activity as the natural sequences. Consequently, these synthetic mutant and modified forms of the genes and expression products of these genes are also meant to be encompassed by the present invention.

All patents and publications referred to above are incorporated by reference herein.

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Claims

1. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn biosynthetic enzyme, wherein said enzyme is defined by an amino acid sequence selected from the group consisting of SEQ ID NOS 2-5, 7-24, 26, 27, 29, 33, or said enzyme is defined by an amino acid selected from SEQ ID NOS 2-5, 7-24, 26, 27, 29, 33 in which one or more amino acid substitutions have been made that do not affect the functional properties of the enzyme.

2. An isolated DNA molecule of claim 1 wherein said DNA sequence is selected from the group of genes consisting of *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, ORFL15, ORFL16, ORFR1, ORFR2, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, and *S. spinosa kre*, said genes being described by bases 21111-28898, 28916-35374, 35419-44931, 44966-59752, 59803-76569, 20168-20995, 18541-19713, 17749-18501, 16556-17743, 14799-16418, 13592-14785, 12696-13547, 11530-12492, 10436-11434, 8967-10427, 7083-8450, 5363-6751, 4168-5325, 3416-4165, 2024-2791, 1135-1971, 76932-77528, and 77729-79984 of SEQ ID NO:1, bases 334-1119 of SEQ ID NO:27, bases 88-1077 of SEQ ID NO 24, bases 226-834 of SEQ ID NO 31, and bases 1165-1992 of SEQ ID NO:24.

3. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain, where said domain is selected from KSi, ATi, ACPi, KS1, AT1, KR1, and ACP1, corresponding, respectively, to amino acid sequences 6-423, 528-853, 895-977, 998-1413, 1525-1858, 2158-2337, and 2432-2513 of SEQ ID NO:2, or said domain is one of said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

4. An isolated DNA molecule of claim 3 wherein said DNA sequence is selected from the group consisting of bases 21126-22379, 22692-23669, 23793-24041, 24102-25349, 25683-26684, 27582-28121, and 28404-28649 of SEQ ID NO:1.

5. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain, where said domain is selected from KS2, AT2, DH2, ER2, KR2, and ACP2, corresponding, respectively, to amino acid sequences 1-424, 536-866, 892-1077, 1338-1683, 1687-1866, and 1955-2034 of SEQ ID NO:3, or said domain is one of

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said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

6. An isolated DNA molecule of claim 5 wherein said DNA sequence is selected from the group consisting of bases 29024-30295, 30629-31621, 31697-32254, 33035-34072, 34082-34621, 34886-35125 of SEQ ID NO:1.

7. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain, where said domain is selected from KS3, AT3, KR3, ACP3, KS4, AT4, KR4, and ACP4, corresponding, respectively, to amino acid sequences 1-423, 531-280, 1159-1337, 1425-1506, 1529-1952, 2066-2396, 2700-2880, and 2972-3053 of SEQ ID NO:4, or said domain is one of said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

8. An isolated DNA molecule of claim 7 wherein said DNA sequence is selected from the group consisting of bases 35518-36786, 37108-38097, 38992-39528, 39790-40035, 40102-41373, 41713-42705, 43615-44157, and 44431-44676 of SEQ ID NO:1.

9. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain, where said domain is selected from KS5, AT5, DH5, KR5, ACP5, KS6, AT6, KR6, ACP6, KS7, AT7, KR7, and ACP7, corresponding, respectively to amino acid sequences 1-424, 539-866, 893-1078, 1384-1565, 1645-1726, 1748-2172, 2283-2613, 2916-3095, 3188-3269, 3291-3713, 3825-4153, 4344-4638, and 4725-4806 of SEQ ID NO:5, or said domain is one of said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

10 An isolated DNA molecule of claim 9 wherein said DNA sequence is selected from the group consisting of bases 45077-46348, 46691-47674, 47753-48310, 49226-49771, 50009-50254, 50318-51592, 51923-52915, 53822-54361, 54638-54883, 54947-56215, 56549-57535, 58106-58990, and 59249-59494 of SEQ ID NO:1.

11 An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS domain, where said domain is selected from KS8, AT8, DH8, KR8, ACP8, KS9, AT9, DH9, KR9, ACP9, KS10, AT10, DH10, KR10, ACP10, and TE10, corresponding, respectively, to amino acid sequences 1-424, 530-848, 883-1070, 1369-

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1552, 1648-1726, 1749-2173, 2287-2614, 2640-2800, 3157-3341, 3422-3500, 3534-3948, 4060-4390, 4413-4597, 4900-5078, 5172-5253, and 5302-5555 of SEQ ID NO:6, or said domain is one of said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

12. An isolated DNA molecule of claim 11 wherein said DNA sequence is selected from the group consisting of bases 59902-61173, 61489-62445, 62548-63111, 64006-64557, 64843-65079, 65146-66420, 66760-67743, 67819-68301, 69370-69924, 70165-70401, 70471-71745, 72079-73071, 73138-73692, 74599-75135, 75415-75660, and 75805-76566 of SEQ ID NO:1.

13. An isolated DNA molecule comprising a DNA sequence that encodes a spinosyn PKS module, where said module is selected from the group consisting of amino acid sequences 6-1413 of SEQ ID NO:2, 1525-2513 of SEQ ID NO:2, 1-2034 of SEQ ID NO:3, 1-1506 of SEQ ID NO:4, 1529-3053 of SEQ ID NO:4, 1-1726 of SEQ ID NO:5, 1748-3269 of SEQ ID NO:5, 3291-4806 of SEQ ID NO:5, 1-1726 of SEQ ID NO:5, 1-1726 of SEQ ID NO:6, 1749-3500 of SEQ ID NO:6, and 35434-5555 of SEQ ID NO:6, or said module is one of the said amino acid sequences in which one or more amino acid substitutions have been made that do not affect the functional properties of the domain.

14. An isolated DNA molecule of claim 13 wherein said DNA sequence is selected from the group consisting of bases 21126-24041, 24102-28649, 29024-35125, 35518-40035, 40102-44676, 45077-50254, 50318-54883, 54947-59494, 59902-65079, 65146-70401, and 70471-76566 of SEQ ID NO:1.

15. A recombinant DNA vector which comprises a DNA sequence as defined in claim 1.

16. A host cell transformed with a recombinant vector as claimed in claim 15.

17. A method of producing spinosyn in increased amounts comprising the steps of:

1) transforming with a recombinant DNA vector or portion thereof a microorganism that produces spinosyn or a spinosyn precurser by means of a biosynthetic pathway, said vector or portion thereof comprising a DNA sequence of claim 1 that codes for the expression of an activity that is rate limiting in said pathway, and

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2) culturing said microorganism transformed with said vector under conditions suitable for cell growth and division, expression of said DNA sequence, and production of spinosyn.

18. A method of claim 17 wherein step 1) comprises transforming said microorganism with a vector or portion thereof comprising a DNA sequence that codes for *S. spinosa gtt* and *S. spinosa gdh.*

19. A transformed spinosyn-producing microorganism having spinosyn biosynthetic genes in its genome wherein at least one of the spinosyn biosynthetic genes, selected from *spnA*, *spnB*, *spnC*, *spnD*, *spnE*, *spnF*, *spnG*, *spnH*, *spnI*, *spnJ*, *spnK*, *spnL*, *spnM*, *spnN*, *spnO*, *spnP*, *spnQ*, *spnR*, *spnS*, *S. spinosa gtt*, *S. spinosa gdh*, *S. spinosa epi*, and *S. spinosa kre*, is duplicated.

20. A transformed spinosyn producing microorganism of claim 19 wherein *S. spinosa gtt* and S. *spinosa gdh* are duplicated.

21. A process for producing a spinosyn compound which comprises cultivating a transformed spinosyn-producing microorganism of claim 20.

22. A transformed spinosyn producing microorganism of claim 19 wherein *S. spinosa gtt*, S. *spinosa gdh*, and *S. spinosa kre* are duplicated.

23. A process for producing a spinosyn compound which comprises cultivating a transformed spinosyn-producing microorganism of claim 22.

24. A process for producing a spinosyn compound which comprises cultivating a transformed spinosyn-producing microorganism of claim 19.

25. A transformed spinosyn-producing microorganism having spinosyn biosynthetic genes in its genome, wherein at least one of said genes has been disrupted by recombination with an internal fragment of that gene, the rest of said genes being operational to produce a spinosyn other than the one that would be produced if the disrupted gene were operational.

26. A process for producing a spinosyn compound which comprises cultivating a transformed spinosyn-producing microorganism of claim 25.

27. A transformed spinosyn-producing microorganism having operational spinosyn biosynthetic genes including multiple PKS modules in its genome, wherein said genes a) include at least one operational PKS module more or at least one less than is present in SEQ ID NO:1; or b) include a PKS module that differs from the corresponding

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module described in SEQ ID NO:1 by the deletion, inactivation, or addition of a KR, DH or ER domain, or by the substitution of an AT domain that specifies a different carboxylic acid.

28. A process for producing a spinosyn which comprises cultivating a transformed spinosyn-producing microorganism of claim 27.

29. A process for isolating a macrolide biosynthetic gene which comprises creating a genomic library of a macrolide producing microorganism, and using a labeled fragment of SEQ ID NO:1, SEQ ID NO:25, SEQ ID NO:28, or SEQ ID NO:32 that is at least 20 bases long as a hybridization probe.

30. A process of claim 29 wherein the microorganism is a spinosyn producing microorganism.

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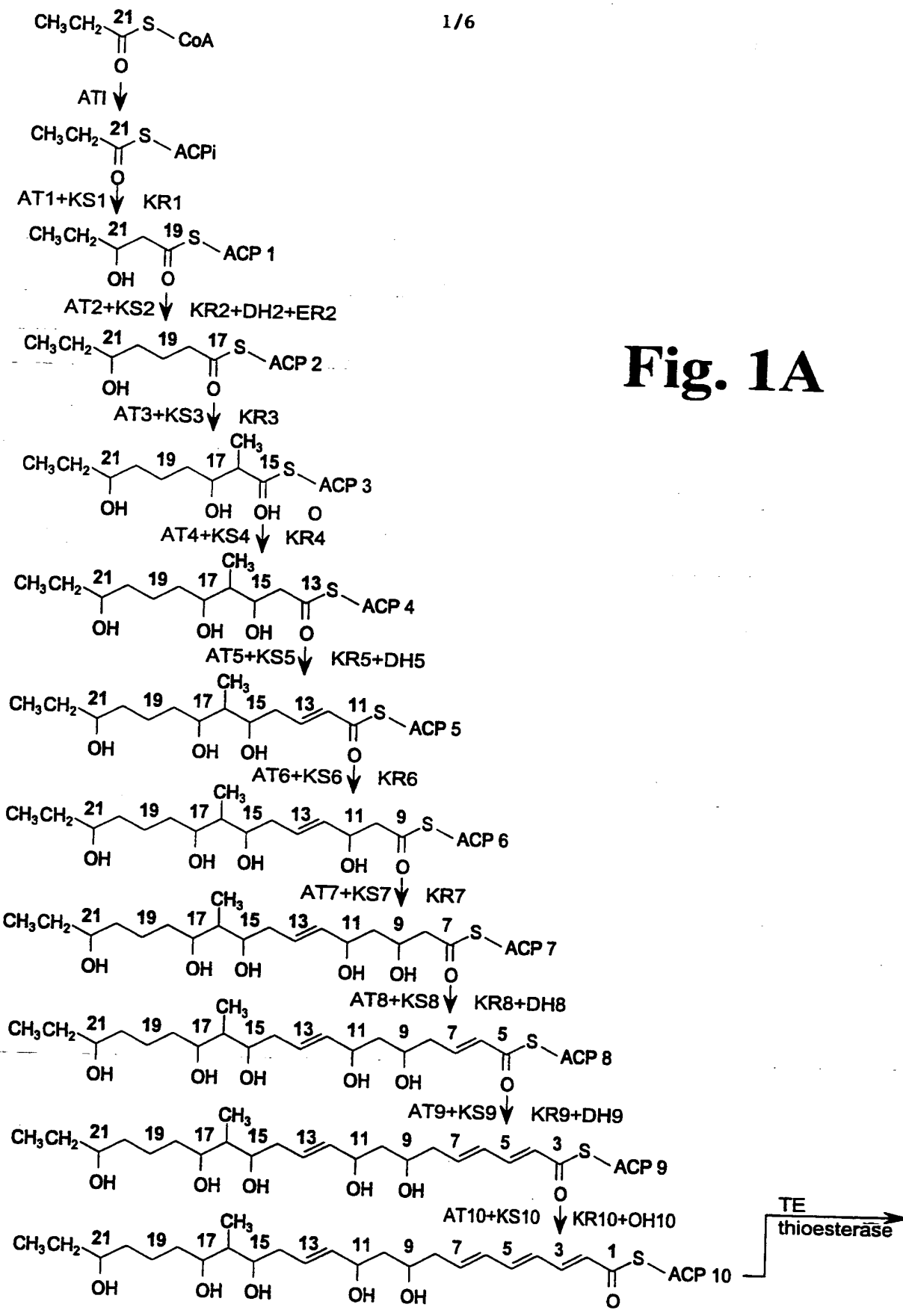

Fig. 1A

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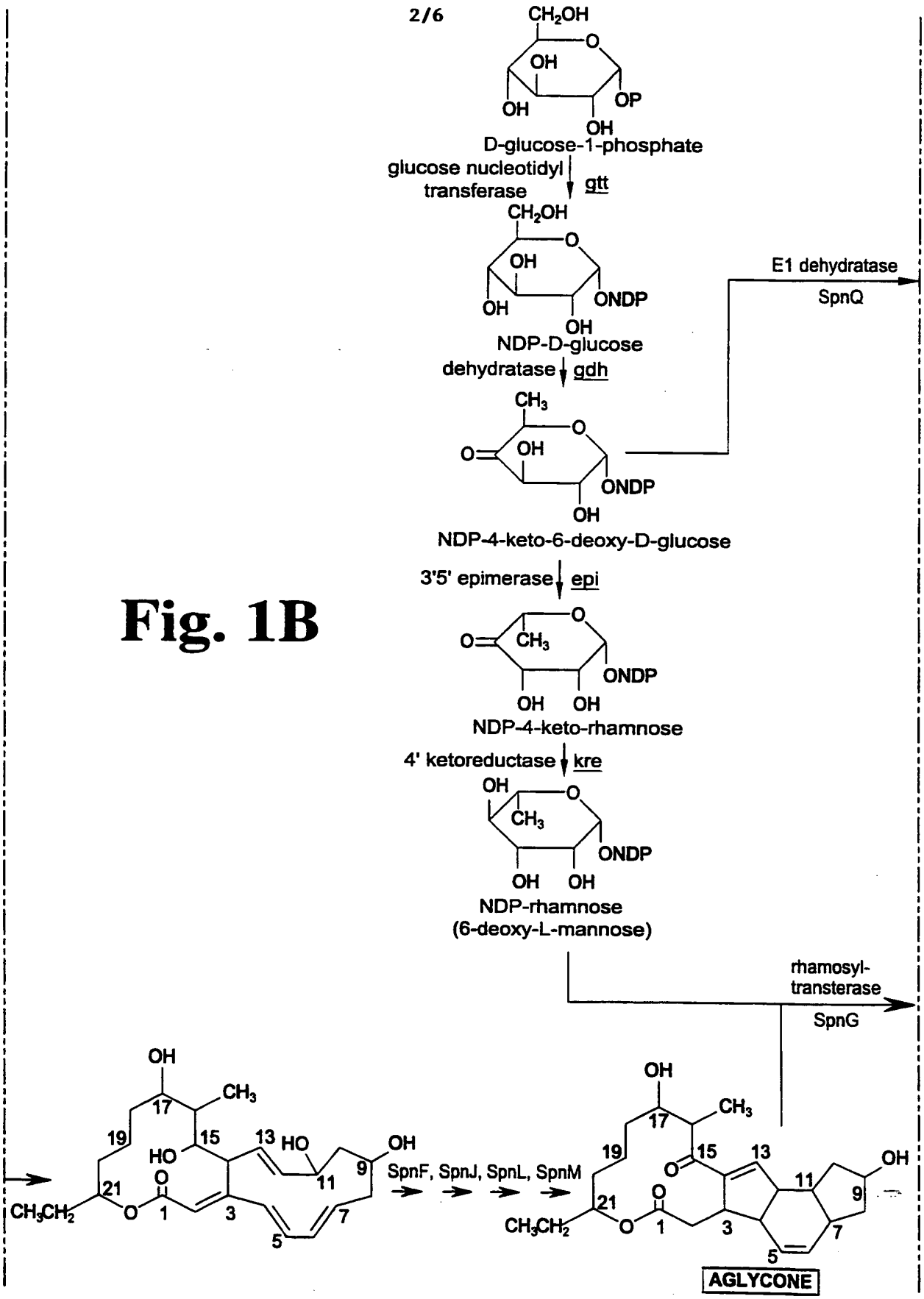

Fig. 1B

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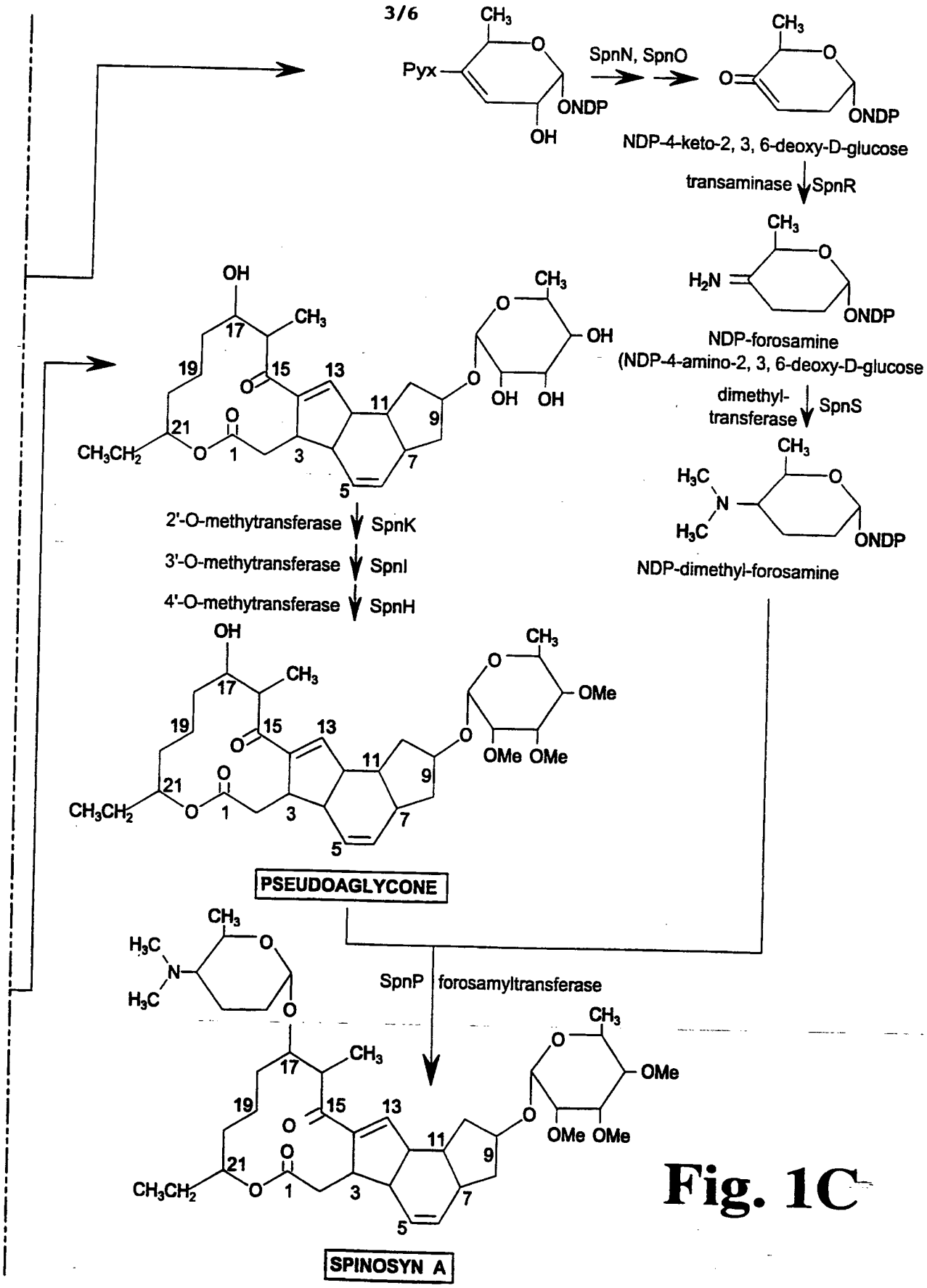

Fig. 1C

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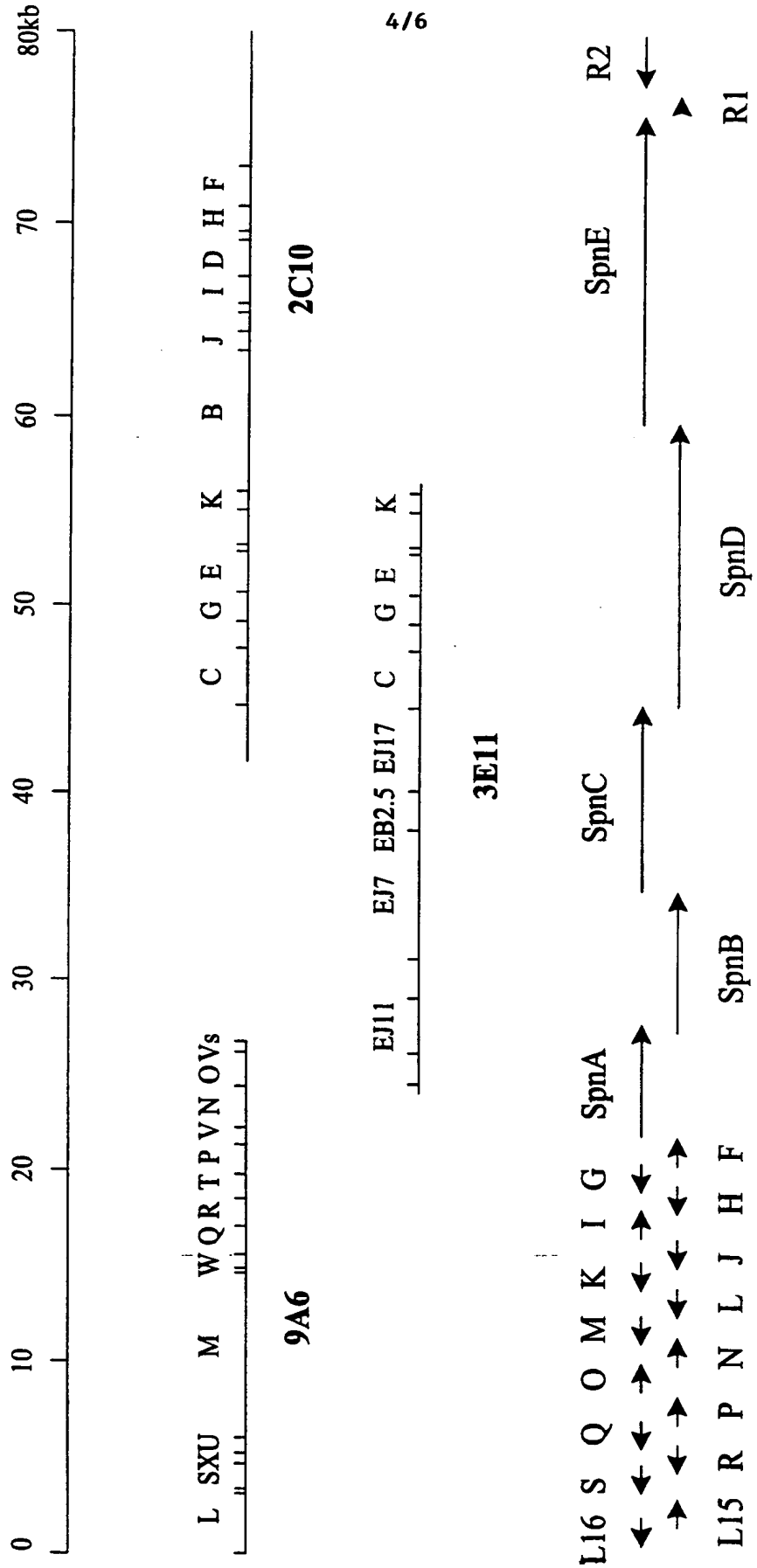

Fig. 2

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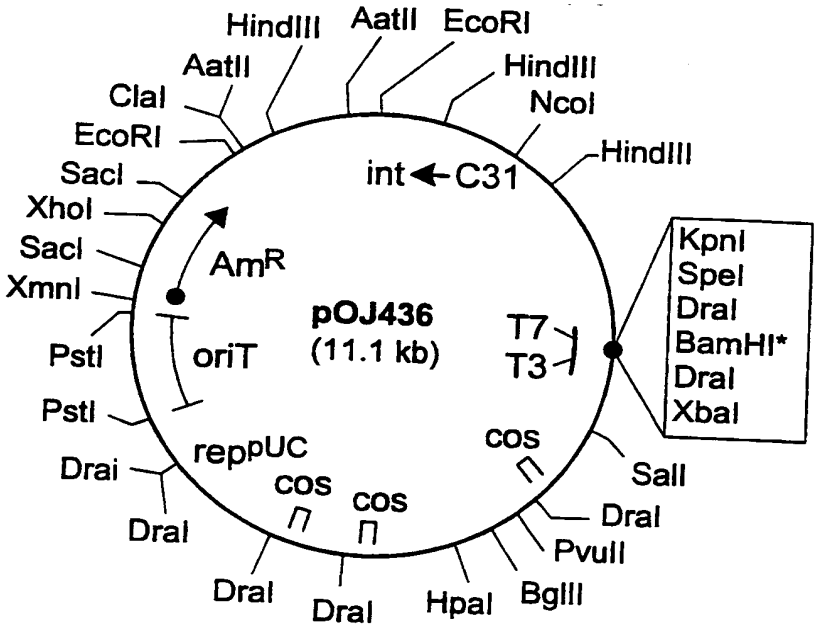

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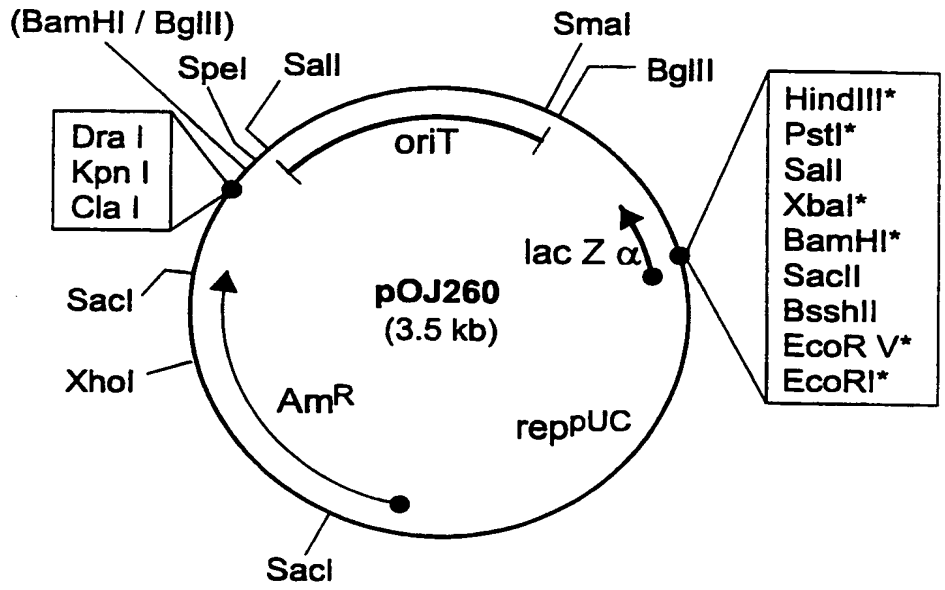

Fig. 4

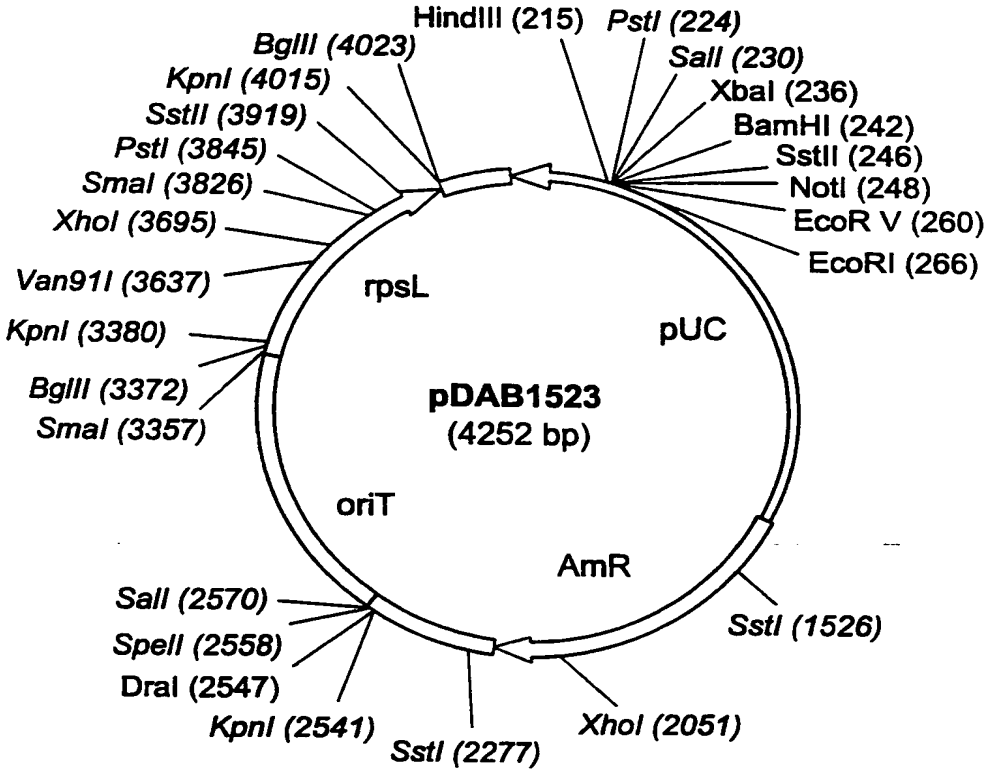

Fig 5

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ccgtcctttt tccaccgaca acacgtatca cgaacggctg tcaagcaaac cggcggtcac 80020
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aggtgccgct ggctccagat c 80161

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Leu Pro Gln Ala Pro Asp Pro Ala Ser Phe Trp Arg Leu Leu Arg Thr
20 25 30

Gly Thr Asp Ala Ile Thr Thr Val Pro Glu Gly Arg Trp Gly Asp Pro
35 40 45

BNSDOCID: <WO___9946387A1_I_>

Leu Pro Gly Arg Asp Ala Pro Lys Gly Pro Glu Trp Gly Gly Phe Leu
50 55 60

Ala Asp Val Asp Cys Phe Asp Pro Glu Phe Phe Gly Ile Ser Pro Arg
65 70 75 80

Glu Ala Ala Thr Val Asp Pro Gln Gln Arg Leu Ala Leu Glu Leu Ala
85 90 95

Trp Glu Ala Leu Glu Asp Ala Gly Ile Pro Ala Gly Glu Leu Arg Gly
100 105 110

Thr Ala Ala Gly Val Phe Met Gly Ala Ile Ser Asp Asp Tyr Ala Ala
115 120 125

Leu Leu Arg Glu Ser Pro Pro Glu Val Ala Ala Gln Tyr Arg Leu Thr
130 135 140

Gly Thr His Arg Ser Leu Ile Ala Asn Arg Val Ser Tyr Val Leu Gly
145 150 155 160

Leu Arg Gly Pro Ser Leu Thr Val Asp Ser Gly Gln Ser Ser Ser Leu
165 170 175

Val Gly Val His Leu Ala Ser Glu Ser Leu Arg Arg Gly Glu Cys Thr
180 185 190

Ile Ala Leu Ala Gly Gly Val Asn Leu Asn Leu Ala Ala Glu Ser Asn
195 200 205

Ser Ala Leu Met Asp Phe Gly Ala Leu Ser Pro Asp Gly Arg Cys Phe
210 215 220

Thr Phe Asp Val Arg Ala Asn Gly Tyr Val Arg Gly Glu Gly Gly Gly
225 230 235 240

Leu Val Val Leu Lys Lys Ala Asp Gln Ala His Ala Asp Gly Asp Arg
245 250 255

Ile Tyr Cys Leu Ile Arg Gly Ser Ala Val Asn Asn Asp Gly Gly Gly
260 265 270

Ala Gly Leu Thr Val Pro Ala Ala Asp Ala Gln Ala Glu Leu Leu Arg
275 280 285

Gln Ala Tyr Arg Asn Ala Gly Val Asp Pro Ala Ala Val Gln Tyr Val
290 295 300

Glu Leu His Gly Ser Ala Thr Arg Val Gly Asp Pro Val Glu Ala Ala
305 310 315 320

Ala Leu Gly Ala Val Leu Gly Ala Ala Arg Arg Pro Gly Asp Glu Leu
325 330 335

Arg Val Gly Ser Ala Lys Thr Asn Val Gly His Leu Glu Ala Ala Ala
340 345 350

Gly Val Thr Gly Leu Leu Lys Thr Ala Leu Ser Ile Trp His Arg Glu

BNSDOCID: <WO___9946387A1_I_>

355 360 365

Leu Pro Pro Ser Leu His Phe Thr Ala Pro Asn Pro Glu Ile Pro Leu
370 375 380

Asp Glu Leu Asn Leu Arg Val Gln Arg Asp Leu Arg Pro Trp Pro Glu
385 390 395 400

Ser Glu Gly Pro Leu Leu Ala Gly Val Ser Ala Phe Gly Met Gly Gly
405 410 415

Thr Asn Cys His Leu Val Leu Ser Gly Thr Ser Arg Val Glu Arg Arg
420 425 430

Arg Ser Gly Pro Ala Glu Ala Thr Met Pro Trp Val Leu Ser Ala Arg
435 440 445

Thr Pro Val Ala Leu Arg Ala Gln Ala Ala Arg Leu His Thr His Leu
450 455 460

Asn Thr Ala Gly Gln Ser Pro Leu Asp Val Ala Tyr Ser Leu Ala Thr
465 470 475 480

Thr Arg Ser Ala Leu Pro His Arg Ala Ala Leu Val Ala Asp Asp Glu
485 490 495

Pro Lys Leu Leu Ala Gly Leu Lys Ala Leu Ala Asp Gly Asp Asp Ala
500 505 510

Pro Thr Leu Cys His Gly Ala Thr Ser Gly Glu Arg Ala Ala Val Phe
515 520 525

Val Phe Pro Gly Gln Gly Ser Gln Trp Ile Gly Met Gly Arg Gln Leu
530 535 540

Leu Glu Thr Ser Glu Val Phe Ala Ala Ser Met Ser Asp Cys Ala Asp
545 550 555 560

Ala Leu Ala Pro His Leu Asp Trp Ser Leu Leu Asp Val Leu Arg Asn
565 570 575

Ala Ala Gly Ala Ala His Leu Asp His Asp Asp Val Val Gln Pro Ala
580 585 590

Leu Phe Ala Ile Met Val Ser Leu Ala Glu Leu Trp Arg Ser Trp Gly
595 600 605

Val Arg Pro Val Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala
610 615 620

Ala Cys Val Ala Gly Ala Leu Ser Val Arg Asp Ala Ala Arg Val Val
625 630 635 640

Ala Val Arg Ser Arg Leu Leu Thr Ala Leu Ala Gly Ser Gly Ala Met
645 650 655

Ala Ser Leu Gln His Pro Ala Glu Glu Val Arg Gln Ile Leu Leu Pro
660 665 670

BNSDOCID: <WO___9946387A1_I_>

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Trp Arg Asp Arg Ile Gly Val Ala Gly Val Asn Gly Pro Ser Ser Thr
        675                 680                 685

Leu Val Ser Gly Asp Arg Glu Ala Met Ala Glu Leu Leu Ala Glu Cys
    690                 695                 700

Ala Asp Arg Glu Leu Arg Met Arg Arg Ile Pro Val Glu Tyr Ala Ser
705                 710                 715                 720

His Ser Pro His Ile Glu Val Val Arg Asp Glu Leu Leu Gly Leu Leu
                725                 730                 735

Ala Pro Val Glu Pro Arg Thr Gly Ser Ile Pro Ile Tyr Ser Thr Thr
            740                 745                 750

Thr Gly Asp Leu Leu Asp Arg Pro Met Asp Ala Asp Tyr Trp Tyr Arg
        755                 760                 765

Asn Leu Arg Gln Pro Val Leu Phe Glu Ala Ala Val Glu Ala Leu Leu
    770                 775                 780

Lys Arg Gly Tyr Asp Ala Phe Ile Glu Ile Ser Pro His Pro Val Leu
785                 790                 795                 800

Thr Ala Asn Ile Gln Glu Thr Ala Val Arg Ala Gly Arg Glu Val Val
                805                 810                 815

Ala Leu Gly Thr Leu Arg Arg Gly Glu Gly Gly Met Arg Gln Ala Leu
            820                 825                 830

Thr Ser Leu Ala Arg Ala His Val His Gly Val Ala Ala Asp Trp His
        835                 840                 845

Ala Val Phe Ala Gly Thr Gly Ala Gln Arg Val Asp Leu Pro Thr Tyr
    850                 855                 860

Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ala Lys Leu Pro Asp Val
865                 870                 875                 880

Ala Met Pro Glu Ser Asp Val Ser Thr Ala Leu Arg Glu Lys Leu Arg
                885                 890                 895

Ser Ser Pro Arg Ala Asp Val Asp Ser Thr Thr Leu Thr Met Ile Arg
            900                 905                 910

Ala Gln Ala Ala Val Val Leu Gly His Ser Asp Pro Lys Glu Val Asp
        915                 920                 925

Pro Asp Arg Thr Phe Lys Asp Leu Gly Phe Asp Ser Ser Met Val Val
    930                 935                 940

Glu Leu Cys Asp Arg Leu Asn Ala Ala Thr Gly Leu Arg Leu Ala Pro
945                 950                 955                 960

Ser Val Val Phe Asp Cys Pro Thr Pro Asp Lys Leu Ala Arg Gln Val
                965                 970                 975
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BNSDOCID: <WO___9946387A1_I_>

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Arg Thr Leu Leu Leu Gly Glu Pro Ala Pro Met Thr Ser His Arg Pro
            980                 985                 990

Asp Ser Asp Ala Asp Glu Pro Ile Ala Val Ile Gly Met Gly Cys Arg
        995                1000                1005

Phe Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Gln Leu Val Ala
   1010                1015                1020

Ala Gly Arg Asp Val Val Ser Glu Phe Pro Ala Asp Arg Gly Trp Asp
1025                1030                1035                1040

Leu Glu Arg Ala Gly Thr Ser His Val Arg Ala Gly Gly Phe Leu His
                1045                1050                1055

Gly Ala Pro Asp Phe Asp Pro Gly Phe Phe Arg Ile Ser Pro Arg Glu
            1060                1065                1070

Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Ile Ala Trp
        1075                1080                1085

Glu Ala Val Glu Arg Gly Gly Ile Asn Pro Gln His Leu His Gly Ser
   1090                1095                1100

Gln Thr Gly Val Phe Val Gly Ala Thr Ser Leu Asp Tyr Gly Pro Arg
1105                1110                1115                1120

Leu His Glu Ala Ser Glu Glu Ala Ala Gly Tyr Val Leu Thr Gly Ser
                1125                1130                1135

Thr Thr Ser Val Ala Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu
            1140                1145                1150

Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala
        1155                1160                1165

Leu His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala
   1170                1175                1180

Leu Ala Gly Gly Val Thr Val Met Ala Thr Pro Gly Met Phe Val Glu
1185                1190                1195                1200

Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe
                1205                1210                1215

Ala Glu Ala Ala Asp Gly Thr Gly Trp Ser Glu Gly Ala Gly Leu Val
            1220                1225                1230

Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly His Glu Val Leu
        1235                1240                1245

Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly
   1250                1255                1260

Leu Thr Ala Pro Asn Gly Ser Ser Gln Gln Arg Val Ile Ala Gln Ala
1265                1270                1275                1280

Leu Ala Ser Ala Gly Leu Ser Val Ser Asp Val Asp Ala Val Glu Ala
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BNSDOCID: <WO___9946387A1_I_>

1285 1290 1295

His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu
1300 1305 1310

Ile Ala Thr Tyr Gly Gln Gly Arg Leu Pro Glu Arg Pro Leu Trp Leu
1315 1320 1325

Gly Ser Met Lys Ser Asn Ile Gly His Ala Gln Ala Ala Ala Gly Ile
1330 1335 1340

Ala Gly Val Met Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro
1345 1350 1355 1360

Arg Thr Leu His Val Asp Glu Pro Thr Ser Gly Val Asp Trp Ser Ala
1365 1370 1375

Gly Thr Val Gln Leu Leu Thr Glu Asn Thr Pro Trp Pro Gly Ser Gly
1380 1385 1390

Arg Val Arg Arg Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn
1395 1400 1405

Ala His Val Ile Leu Glu Gln Pro Pro Gly Val Pro Ser Gln Ser Ala
1410 1415 1420

Gly Pro Gly Ser Gly Ser Val Val Asp Val Pro Val Val Pro Trp Met
1425 1430 1435 1440

Val Ser Gly Lys Thr Pro Glu Ala Leu Ser Ala Gln Ala Thr Ala Leu
1445 1450 1455

Met Thr Tyr Leu Asp Glu Arg Pro Asp Val Ser Ser Leu Asp Val Gly
1460 1465 1470

Tyr Ser Leu Ala Leu Thr Arg Ser Ala Leu Asp Glu Arg Ala Val Val
1475 1480 1485

Leu Gly Ser Asp Arg Glu Thr Leu Leu Cys Gly Val Lys Ala Leu Ser
1490 1495 1500

Ala Gly His Glu Ala Ser Gly Leu Val Thr Gly Ser Val Gly Ala Gly
1505 1510 1515 1520

Gly Arg Ile Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly
1525 1530 1535

Met Gly Arg Gly Leu Tyr Arg Ala Phe Pro Val Phe Ala Ala Ala Phe
1540 1545 1550

Asp Glu Ala Cys Ala Glu Leu Asp Ala His Leu Gly Gln Glu Ile Gly
1555 1560 1565

Val Arg Glu Val Val Ser Gly Ser Asp Ala Gln Leu Leu Asp Arg Thr
1570 1575 1580

Leu Trp Ala Gln Ser Gly Leu Phe Ala Leu Gln Val Gly Leu Leu Lys
1585 1590 1595 1600

BNSDOCID: <WO___9946387A1_I_>

Leu Leu Asp Ser Trp Gly Val Arg Pro Ser Val Val Leu Gly His Ser
1605 1610 1615

Val Gly Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Val Ser Leu Ser
1620 1625 1630

Gly Ala Ala Arg Leu Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu
1635 1640 1645

Pro Ser Gly Gly Gly Met Leu Ala Val Pro Ala Gly Glu Glu Leu Leu
1650 1655 1660

Trp Ser Leu Leu Ala Asp Gln Gly Asp Arg Val Gly Ile Ala Ala Val
1665 1670 1675 1680

Asn Ala Ala Gly Ser Val Val Leu Ser Gly Asp Arg Asp Val Leu Asp
1685 1690 1695

Asp Leu Ala Gly Arg Leu Asp Gly Gln Gly Ile Arg Ser Arg Trp Leu
1700 1705 1710

Arg Val Ser His Ala Phe His Ser Tyr Arg Met Asp Pro Met Leu Ala
1715 1720 1725

Glu Phe Ala Glu Leu Ala Arg Thr Val Asp Tyr Arg Arg Cys Glu Val
1730 1735 1740

Pro Ile Val Ser Thr Leu Thr Gly Asp Leu Asp Asp Ala Gly Arg Met
1745 1750 1755 1760

Ser Gly Pro Asp Tyr Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe
1765 1770 1775

Ala Asp Gly Val Gln Ala Leu Val Glu His Asp Val Ala Thr Val Val
1780 1785 1790

Glu Leu Gly Pro Asp Gly Ala Leu Ser Ala Leu Ile Gln Glu Cys Val
1795 1800 1805

Ala Ala Ser Asp His Ala Gly Arg Leu Ser Ala Val Pro Ala Met Arg
1810 1815 1820

Arg Asn Gln Asp Glu Ala Gln Lys Val Met Thr Ala Leu Ala His Val
1825 1830 1835 1840

His Val Arg Gly Gly Ala Val Asp Trp Arg Ser Phe Phe Ala Gly Thr
1845 1850 1855

Arg Ala Lys Gln Ile Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg
1860 1865 1870

Tyr Trp Leu Asn Ala Leu Arg Glu Ser Ser Ala Gly Asp Met Gly Arg
1875 1880 1885

Arg Val Glu Ala Lys Phe Trp Gly Ala Val Glu His Glu Asp Val Glu
1890 1895 1900

BNSDOCID: <WO___9946387A1_I_>

Ser Leu Ala Arg Val Leu Gly Ile Val Asp Asp Gly Ala Ala Val Asp
1905 1910 1915 1920

Ser Leu Arg Ser Ala Leu Pro Val Leu Ala Gly Trp Gln Arg Thr Arg
1925 1930 1935

Thr Thr Glu Ser Ile Met Asp Pro Arg Cys Tyr Arg Ile Gly Trp Arg
1940 1945 1950

Gln Val Ala Gly Leu Pro Pro Met Gly Thr Val Phe Gly Thr Trp Leu
1955 1960 1965

Val Phe Ala Pro His Gly Trp Ser Ser Glu Pro Glu Val Val Asp Cys
1970 1975 1980

Val Thr Ala Leu Arg Ala Arg Gly Ala Ser Val Val Leu Val Glu Ala
1985 1990 1995 2000

Asp Pro Asp Pro Thr Ser Phe Gly Asp Arg Val Arg Thr Leu Cys Ser
2005 2010 2015

Gly Leu Pro Asp Leu Val Gly Val Leu Ser Met Leu Cys Leu Glu Glu
2020 2025 2030

Ser Val Leu Pro Gly Phe Ser Ala Val Ser Arg Gly Phe Ala Leu Thr
2035 2040 2045

Val Glu Leu Val Arg Val Leu Arg Ala Ala Gly Ala Thr Ala Arg Leu
2050 2055 2060

Trp Leu Leu Thr Cys Gly Gly Val Ser Val Gly Asp Val Pro Val Arg
2065 2070 2075 2080

Pro Ala Gln Ala Leu Ala Trp Gly Leu Gly Arg Val Val Gly Leu Glu
2085 2090 2095

His Pro Asp Trp Trp Gly Gly Leu Ile Asp Ile Pro Val Leu Phe Asp
2100 2105 2110

Glu Asp Ala Gln Glu Arg Leu Ser Ile Val Leu Ala Gly Leu Asp Glu
2115 2120 2125

Asp Glu Val Ala Ile Arg Pro Asp Gly Met Phe Ala Arg Arg Leu Val
2130 2135 2140

Arg His Thr Val Ser Ala Asp Val Lys Lys Ala Trp Arg Pro Arg Gly
2145 2150 2155 2160

Ser Val Leu Val Thr Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala
2165 2170 2175

Arg Trp Leu Ala Asp Ala Gly Ala Glu His Val Ala Met Val Ser Arg
2180 2185 2190

Arg Gly Glu Gln Ala Pro Ser Ala Glu Lys Leu Arg Thr Glu Leu Glu
2195 2200 2205

Asp Leu Gly Thr Arg Val Ser Ile Val Ser Cys Asp Val Thr Asp Arg

BNSDOCID: <WO___9946387A1_I_>

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   2210                2215                2220

Glu Ala Leu Ala Glu Val Leu Lys Ala Leu Pro Ala Glu Asn Pro Leu
2225                2230                2235                2240

Thr Ala Val Val His Ala Ala Gly Val Ile Glu Thr Gly Asp Ala Ala
                2245                2250                2255

Ala Met Ser Leu Ala Asp Phe Asp His Val Leu Ser Ala Lys Val Ala
            2260                2265                2270

Gly Ala Ala Asn Leu Asp Ala Leu Leu Ala Asp Val Glu Leu Asp Ala
        2275                2280                2285

Phe Val Leu Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly His
    2290                2295                2300

Gly Ala Tyr Ala Ala Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Gln
2305                2310                2315                2320

Arg Arg Ser Arg Gly Leu Val Ala Thr Ala Val Ala Trp Gly Pro Trp
                2325                2330                2335

Ala Gly Glu Gly Met Ala Ser Gly Glu Thr Gly Asp Gln Leu Arg Arg
            2340                2345                2350

Tyr Gly Leu Ser Pro Met Ala Pro Gln His Ala Ile Ala Gly Ile Arg
        2355                2360                2365

Gln Ala Val Glu Gln Asp Glu Ile Ser Leu Val Val Ala Asp Val Asp
    2370                2375                2380

Trp Ala Arg Phe Ser Ala Gly Leu Leu Ala Ala Arg Pro Arg Pro Leu
2385                2390                2395                2400

Leu Asn Glu Leu Ala Glu Val Lys Glu Leu Leu Val Asp Ala Gln Pro
                2405                2410                2415

Glu Ala Gly Val Leu Ala Asp Ala Ser Leu Glu Trp Arg Gln Arg Leu
            2420                2425                2430

Ser Ala Ala Pro Arg Pro Thr Gln Glu Gln Leu Ile Leu Glu Leu Val
        2435                2440                2445

Arg Gly Glu Thr Ala Leu Val Leu Gly His Pro Gly Ala Ala Ala Val
    2450                2455                2460

Ala Ser Glu Arg Ala Phe Lys Asp Ser Gly Phe Asp Ser Gln Ala Ala
2465                2470                2475                2480

Val Glu Leu Arg Val Arg Leu Asn Arg Ala Thr Gly Leu Gln Leu Pro
                2485                2490                2495

Ser Thr Ile Ile Phe Ser His Pro Thr Pro Ala Glu Leu Ala Ala Glu
            2500                2505                2510

Leu Arg Ala Arg Leu Leu Pro Glu Ser Ala Gly Ala Gly Ile Pro Glu
        2515                2520                2525
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BNSDOCID: <WO___9946387A1_I_>

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Glu Asp Glu Ala Arg Ile Arg Ala Ala Leu Thr Ser Ile Pro Phe Pro
   2530                2535                2540

Ala Leu Arg Glu Ala Gly Leu Val Ser Pro Leu Leu Ala Leu Ala Gly
2545                2550                2555                2560

His Pro Val Asp Ser Gly Ile Ser Ser Asp Asp Ala Ala Ala Thr Ser
               2565                2570                2575

Ile Asp Ala Met Asp Val Ala Gly Leu Val Glu Ala Ala Leu Gly Glu
           2580                2585                2590

Arg Glu Ser
       2595
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<212> PRT
<213> Saccharopolyspora spinosa

<400> 3

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Met Thr Val Thr Thr Ser Tyr Glu Glu Val Val Glu Ala Leu Arg Ala
  1               5                  10                  15

Ser Leu Lys Glu Asn Glu Arg Leu Arg Arg Gly Arg Asp Arg Phe Ser
             20                  25                  30

Ala Glu Lys Asp Asp Pro Ile Ala Ile Val Ala Met Ser Cys Arg Tyr
         35                  40                  45

Pro Gly Gln Val Ser Ser Pro Glu Asp Leu Trp Gln Leu Ala Ala Gly
     50                  55                  60

Gly Val Asp Ala Ile Ser Glu Val Pro Gly Asp Arg Gly Trp Asp Leu
 65                  70                  75                  80

Asp Gly Val Phe Val Pro Asp Ser Asp Arg Pro Gly Thr Ser Tyr Ala
                 85                  90                  95

Cys Ala Gly Gly Phe Leu Gln Gly Val Ser Glu Phe Asp Ala Gly Phe
            100                 105                 110

Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
        115                 120                 125

Leu Leu Leu Glu Val Ala Trp Glu Val Phe Glu Arg Ala Gly Leu Glu
    130                 135                 140

Gln Arg Ser Thr Arg Gly Ser Arg Val Gly Val Phe Val Gly Thr Asn
145                 150                 155                 160

Gly Gln Asp Tyr Ala Ser Trp Leu Arg Thr Pro Pro Pro Ala Val Ala
                165                 170                 175

Gly His Val Leu Thr Gly Gly Ala Ala Ala Val Leu Ser Gly Arg Val
            180                 185                 190
```


BNSDOCID: <WO___9946387A1_I_>

```
Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala
        195                 200                 205

Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu Arg
    210                 215                 220

Ala Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser
225                 230                 235                 240

Thr Pro Lys Val Phe Leu Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro
                245                 250                 255

Asp Gly Arg Cys Lys Ser Phe Ala Ala Gly Ala Asp Gly Thr Gly Trp
            260                 265                 270

Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg
        275                 280                 285

Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val Asn
    290                 295                 300

Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Ser Ser Gln
305                 310                 315                 320

Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val Ser
                325                 330                 335

Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp
            340                 345                 350

Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg Asp
        355                 360                 365

Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His
    370                 375                 380

Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala
385                 390                 395                 400

Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Glu Ser Pro Ser
                405                 410                 415

Pro Glu Val Asp Trp Ser Ala Gly Thr Val Gln Leu Leu Thr Glu Asn
            420                 425                 430

Thr Pro Trp Pro Arg Ser Gly Arg Val Arg Arg Val Gly Val Ser Ser
        435                 440                 445

Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Pro Pro
    450                 455                 460

Gly Val Pro Ser Gln Ser Ala Gly Pro Gly Ser Gly Ser Val Val Asp
465                 470                 475                 480

Val Pro Val Val Pro Trp Met Val Ser Gly Lys Thr Pro Glu Ala Leu
                485                 490                 495
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BNSDOCID: <WO___9946387A1_I_>

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Ser Ala Gln Ala Thr Ala Leu Met Thr Tyr Leu Asp Glu Arg Pro Asp
            500                 505                 510

Val Ser Ser Leu Asp Val Gly Tyr Ser Leu Ala Leu Thr Arg Ser Ala
        515                 520                 525

Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Glu Thr Leu Leu
    530                 535                 540

Cys Gly Val Lys Ala Leu Ser Ala Gly His Glu Ala Ser Gly Leu Val
545                 550                 555                 560

Thr Gly Ser Val Gly Ala Gly Gly Arg Ile Gly Phe Val Phe Ser Gly
                565                 570                 575

Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu Tyr Arg Ala Phe
            580                 585                 590

Pro Val Phe Ala Ala Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp Ala
        595                 600                 605

His Leu Gly Gln Glu Ile Gly Val Arg Glu Val Val Ser Gly Ser Asp
    610                 615                 620

Ala Gln Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe Ala
625                 630                 635                 640

Leu Gln Val Gly Leu Leu Lys Leu Leu Asp Ser Trp Gly Val Arg Pro
                645                 650                 655

Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe Ala
            660                 665                 670

Ala Gly Val Val Ser Leu Ser Gly Ala Ala Arg Leu Val Ala Gly Arg
        675                 680                 685

Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Gly Met Leu Ala Val
    690                 695                 700

Pro Ala Gly Glu Glu Leu Leu Trp Ser Leu Leu Ala Asp Gln Gly Asp
705                 710                 715                 720

Arg Val Gly Ile Ala Ala Val Asn Ala Ala Gly Ser Val Val Leu Ser
                725                 730                 735

Gly Asp Arg Asp Val Leu Asp Asp Leu Ala Gly Arg Leu Asp Gly Gln
            740                 745                 750

Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser Tyr
        755                 760                 765

Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Thr Val
    770                 775                 780

Asp Tyr Arg Arg Cys Glu Val Pro Ile Val Ser Thr Leu Thr Gly Asp
785                 790                 795                 800

Leu Asp Asp Ala Gly Arg Met Ser Gly Pro Asp Tyr Trp Val Arg Gln
```


BNSDOCID: <WO___9946387A1_I_>

805 810 815

Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val Glu
820 825 830

His Asp Val Ala Thr Val Val Glu Leu Gly Pro Asp Gly Ala Leu Ser
835 840 845

Ala Leu Ile Gln Glu Cys Val Ala Ala Ser Asp His Ala Gly Arg Leu
850 855 860

Ser Ala Val Pro Ala Met Arg Arg Asn Gln Asp Glu Ala Gln Lys Val
865 870 875 880

Met Thr Ala Leu Ala His Val His Val Arg Gly Gly Ala Val Asp Trp
885 890 895

Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Ile Glu Leu Pro Thr
900 905 910

Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Val Pro Ser Asp Ser Gly
915 920 925

Asp Val Thr Gly Ala Gly Leu Ala Gly Ala Glu His Pro Leu Leu Gly
930 935 940

Ala Val Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg
945 950 955 960

Ile Ser Val Arg Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly
965 970 975

Glu Val Ile Val Ala Gly Thr Ala Leu Leu Glu Ile Ala Leu His Ala
980 985 990

Gly Glu Arg Leu Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala
995 1000 1005

Pro Leu Val Leu Pro Glu Arg Gly Ala Ile Gln Val Gln Leu Arg Val
1010 1015 1020

Gly Ala Pro Glu Asn Ser Gly Arg Arg Pro Met Ala Leu Tyr Ser Arg
1025 1030 1035 1040

Pro Glu Gly Ala Ala Glu His Asp Trp Thr Arg His Ala Thr Gly Arg
1045 1050 1055

Leu Ala Pro Gly Arg Gly Glu Ala Ala Gly Asp Leu Ala Asp Trp Pro
1060 1065 1070

Ala Pro Gly Ala Leu Pro Val Asp Leu Asp Glu Phe Tyr Arg Asp Leu
1075 1080 1085

Ala Glu Leu Gly Leu Glu Tyr Gly Pro Ile Phe Gln Gly Leu Lys Ala
1090 1095 1100

Ala Trp Arg Gln Gly Asp Glu Val Tyr Ala Glu Ala Ala Leu Pro Gly
1105 1110 1115 1120

BNSDOCID: <WO___9946387A1_I_>

Thr Glu Asp Ser Gly Phe Gly Val His Pro Ala Leu Leu Asp Ala Ala
1125 1130 1135

Leu His Ala Thr Ala Val Arg Asp Met Asp Asp Ala Arg Leu Pro Phe
1140 1145 1150

Gln Trp Glu Gly Val Ser Leu His Ala Lys Ala Ala Pro Ala Leu Arg
1155 1160 1165

Val Arg Val Val Pro Ala Gly Asp Asp Ala Lys Ser Leu Leu Val Cys
1170 1175 1180

Asp Gly Thr Gly Arg Pro Val Ile Ser Val Asp Arg Leu Val Leu Arg
1185 1190 1195 1200

Ser Ala Ala Ala Arg Arg Thr Gly Ala Arg Arg Gln Ala His Gln Ala
1205 1210 1215

Arg Leu Tyr Arg Leu Ser Trp Pro Thr Val Gln Leu Pro Thr Ser Ala
1220 1225 1230

Gln Pro Pro Ser Cys Val Leu Leu Gly Thr Ser Glu Val Ser Ala Asp
1235 1240 1245

Ile Gln Val Tyr Pro Asp Leu Arg Ser Leu Thr Ala Ala Leu Asp Ala
1250 1255 1260

Gly Ala Glu Pro Pro Gly Val Val Ile Ala Pro Thr Pro Pro Gly Gly
1265 1270 1275 1280

Gly Arg Thr Ala Asp Val Arg Glu Thr Thr Arg His Ala Leu Asp Leu
1285 1290 1295

Val Gln Gly Trp Leu Ser Asp Gln Arg Leu Asn Glu Ser Arg Leu Leu
1300 1305 1310

Leu Val Thr Gln Gly Ala Val Ala Val Glu Pro Gly Glu Pro Val Thr
1315 1320 1325

Asp Leu Ala Gln Ala Ala Leu Trp Gly Leu Leu Arg Ser Thr Gln Thr
1330 1335 1340

Glu His Pro Asp Arg Phe Val Leu Val Asp Val Pro Glu Pro Ala Gln
1345 1350 1355 1360

Leu Leu Pro Ala Leu Pro Gly Val Leu Ala Cys Gly Glu Pro Gln Leu
1365 1370 1375

Ala Leu Arg Arg Gly Gly Ala His Ala Pro Arg Leu Ala Gly Leu Gly
1380 1385 1390

Ser Asp Asp Val Leu Pro Val Pro Asp Gly Thr Gly Trp Arg Leu Glu
1395 1400 1405

Ala Thr Arg Pro Gly Ser Leu Asp Gly Leu Ala Leu Val Asp Glu Pro
1410 1415 1420

BNSDOCID: <WO___9946387A1_I_>

```
Thr Ala Thr Ala Pro Leu Gly Asp Gly Glu Val Arg Ile Ala Met Arg
1425                1430                1435                1440

Ala Ala Gly Val Asn Phe Arg Asp Ala Leu Ile Ala Leu Gly Met Tyr
                1445                1450                1455

Pro Gly Val Ala Ser Leu Gly Ser Glu Gly Ala Gly Val Val Val Glu
            1460                1465                1470

Thr Gly Pro Gly Val Thr Gly Leu Ala Pro Gly Asp Arg Val Met Gly
        1475                1480                1485

Met Ile Pro Lys Ala Phe Gly Pro Leu Ala Val Ala Asp His Arg Met
    1490                1495                1500

Val Thr Arg Ile Pro Ala Gly Trp Ser Phe Ala Arg Ala Ala Ser Val
1505                1510                1515                1520

Pro Ile Val Phe Leu Thr Ala Tyr Tyr Ala Leu Val Asp Leu Ala Gly
                1525                1530                1535

Leu Arg Pro Gly Glu Ser Leu Leu Val His Ser Ala Ala Gly Gly Val
            1540                1545                1550

Gly Met Ala Ala Ile Gln Leu Ala Arg His Leu Gly Ala Glu Val Tyr
        1555                1560                1565

Ala Thr Ala Ser Glu Asp Lys Trp Gln Ala Val Glu Leu Ser Arg Glu
    1570                1575                1580

His Leu Ala Ser Ser Arg Thr Cys Asp Phe Glu Gln Gln Phe Leu Gly
1585                1590                1595                1600

Ala Thr Gly Gly Arg Gly Val Asp Val Val Leu Asn Ser Leu Ala Gly
                1605                1610                1615

Glu Phe Ala Asp Ala Ser Leu Arg Met Leu Pro Arg Gly Gly Arg Phe
            1620                1625                1630

Leu Glu Leu Gly Lys Thr Asp Val Arg Asp Pro Val Glu Val Ala Asp
        1635                1640                1645

Ala His Pro Gly Val Ser Tyr Gln Ala Phe Asp Thr Val Glu Ala Gly
    1650                1655                1660

Pro Gln Arg Ile Gly Glu Met Leu His Glu Leu Val Glu Leu Phe Glu
1665                1670                1675                1680

Gly Arg Val Leu Glu Pro Leu Pro Val Thr Ala Trp Asp Val Arg Gln
                1685                1690                1695

Ala Pro Glu Ala Leu Arg His Leu Ser Gln Ala Arg His Val Gly Lys
            1700                1705                1710

Leu Val Leu Thr Met Pro Pro Val Trp Asp Ala Ala Gly Thr Val Leu
        1715                1720                1725

Val Thr Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg His Leu
```


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1730 1735 1740

Val Ile Glu Arg Gly Val Arg Asn Leu Val Leu Val Ser Arg Arg Gly
1745 1750 1755 1760

Pro Ala Ala Ser Gly Ala Ala Glu Leu Val Ala Gln Leu Thr Ala Tyr
1765 1770 1775

Gly Ala Glu Val Ser Leu Gln Ala Cys Asp Val Ala Asp Arg Glu Thr
1780 1785 1790

Leu Ala Lys Val Leu Ala Ser Ile Pro Asp Glu His Pro Leu Thr Ala
1795 1800 1805

Val Val His Ala Ala Gly Val Leu Asp Asp Gly Val Ser Glu Ser Leu
1810 1815 1820

Thr Val Glu Arg Leu Asp Gln Val Leu Arg Pro Lys Val Asp Gly Ala
1825 1830 1835 1840

Arg Asn Leu Leu Glu Leu Ile Asp Pro Asp Val Ala Leu Val Leu Phe
1845 1850 1855

Ser Ser Val Ser Gly Val Leu Gly Ser Gly Gly Gln Gly Asn Tyr Ala
1860 1865 1870

Ala Ala Asn Ser Phe Leu Asp Ala Leu Ala Gln Gln Arg Gln Ser Arg
1875 1880 1885

Gly Leu Pro Thr Arg Ser Leu Ala Trp Gly Pro Trp Ala Glu His Gly
1890 1895 1900

Met Ala Ser Thr Leu Arg Glu Ala Glu Gln Asp Arg Leu Ala Arg Ser
1905 1910 1915 1920

Gly Leu Leu Pro Ile Ser Thr Glu Glu Gly Leu Ser Gln Phe Asp Ala
1925 1930 1935

Ala Cys Gly Gly Ala His Thr Val Val Ala Pro Val Arg Phe Ser Arg
1940 1945 1950

Leu Ser Asp Gly Asn Ala Ile Lys Phe Ser Val Leu Gln Gly Leu Val
1955 1960 1965

Gly Pro His Arg Val Asn Lys Ala Ala Thr Ala Asp Asp Ala Glu Ser
1970 1975 1980

Leu Arg Lys Arg Leu Gly Arg Leu Pro Asp Ala Glu Gln His Arg Ile
1985 1990 1995 2000

Leu Leu Asp Leu Val Arg Met His Val Ala Ala Val Leu Gly Phe Ala
2005 2010 2015

Gly Ser Gln Glu Ile Thr Ala Asp Gly Thr Phe Lys Val Leu Gly Phe
2020 2025 2030

Asp Ser Leu Thr Val Val Glu Leu Arg Asn Arg Ile Asn Gly Ala Thr
2035 2040 2045

BNSDOCID: <WO___9946387A1_I_>

```
Gly Leu Arg Leu Pro Ala Thr Leu Val Phe Asn Tyr Pro Thr Pro Asp
   2050                2055                2060

Ala Leu Ala Ala His Leu Val Thr Ala Leu Ser Ala Asp Arg Leu Ala
2065                2070                2075                2080

Gly Thr Phe Glu Glu Leu Asp Arg Trp Ala Ala Asn Leu Pro Thr Leu
                2085                2090                2095

Ala Arg Asp Glu Ala Thr Arg Ala Gln Ile Thr Thr Arg Leu Gln Ala
            2100                2105                2110

Ile Leu Gln Ser Leu Ala Asp Val Ser Gly Gly Thr Gly Gly Gly Ser
        2115                2120                2125

Val Pro Asp Arg Leu Arg Ser Ala Thr Asp Asp Glu Leu Phe Gln Leu
   2130                2135                2140

Leu Asp Asn Asp Leu Glu Leu Pro
2145                2150
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<210> 4
<211> 3170
<212> PRT
<213> Saccharopolyspora spinosa

<400> 4

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Met Ser Asn Glu Glu Lys Leu Arg Glu Tyr Leu Arg Arg Ala Leu Val
  1               5                  10                  15

Asp Leu His Gln Ala Arg Glu Arg Leu His Glu Ala Glu Ser Gly Glu
             20                  25                  30

Arg Glu Pro Ile Ala Ile Val Ala Met Gly Cys Arg Tyr Pro Gly Gly
         35                  40                  45

Val Gln Asp Pro Glu Gly Leu Trp Lys Leu Val Ala Ser Gly Gly Asp
     50                  55                  60

Ala Ile Gly Glu Phe Pro Ala Asp Arg Gly Trp His Leu Asp Glu Leu
 65                  70                  75                  80

Tyr Asp Pro Asp Pro Asp Gln Pro Gly Thr Cys Tyr Thr Arg His Gly
                 85                  90                  95

Gly Phe Leu His Asp Ala Gly Glu Phe Asp Ala Gly Phe Phe Asp Ile
            100                 105                 110

Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
        115                 120                 125

Glu Ile Ser Trp Glu Thr Val Glu Ser Ala Gly Met Asp Pro Arg Ser
    130                 135                 140

Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met Tyr Glu Gly
145                 150                 155                 160
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BNSDOCID: <WO___9946387A1_I_>

Tyr Asp Thr Gly Ala His Arg Ala Gly Glu Gly Val Glu Gly Tyr Leu
165 170 175

Gly Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Ala
180 185 190

Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
195 200 205

Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Gln Gly Glu
210 215 220

Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met Ser Thr Pro Glu
225 230 235 240

Arg Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg
245 250 255

Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
260 265 270

Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
275 280 285

His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly
290 295 300

Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu Ala Gln Glu Arg Val
305 310 315 320

Ile Gln Gln Val Leu Thr Ser Ala Gly Leu Ser Ala Ser Asp Val Asp
325 330 335

Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly Asp Pro Ile Glu
340 345 350

Ala Gln Ala Leu Ile Ala Ala Tyr Gly Gln Asp Arg Asp Arg Asp Arg
355 360 365

Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His Thr Gln Ala
370 375 380

Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met Ala Met Arg His
385 390 395 400

Gly Glu Leu Pro Arg Thr Leu His Val Asp Glu Pro Asn Ser His Val
405 410 415

Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Glu Asn Ile Arg Trp
420 425 430

Pro Gly Thr Gly Thr Arg Arg Ala Gly Val Ser Ser Phe Gly Val Ser
435 440 445

Gly Thr Asn Ala His Val Ile Leu Glu His Asp Pro Leu Ala Val Thr
450 455 460

BNSDOCID: <WO___9946387A1_I_>

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Glu Asn Glu Glu Ala Ala Gln Ser Pro Ala Pro Gly Ile Val Pro Trp
465                 470                 475                 480

Ala Leu Ser Gly Arg Ser Ser Thr Ala Leu Arg Ala Gln Ala Glu Arg
                485                 490                 495

Leu Arg Glu Leu Cys Glu Gln Thr Asp Pro Asp Pro Val Asp Val Gly
            500                 505                 510

Phe Ser Leu Ala Ala Thr Arg Thr Ala Trp Glu His Arg Ala Val Val
        515                 520                 525

Leu Gly Arg Asp Ser Ala Thr Leu Arg Ser Gly Leu Gly Val Val Ala
    530                 535                 540

Ser Gly Glu Pro Ala Val Asp Val Val Glu Gly Ser Val Leu Asp Gly
545                 550                 555                 560

Glu Val Val Phe Val Phe Pro Gly Gln Gly Trp Gln Trp Ala Gly Met
                565                 570                 575

Ala Val Asp Leu Leu Asp Ala Ser Pro Thr Phe Ala Arg His Met Asp
            580                 585                 590

Glu Cys Ala Thr Ala Leu Arg Arg Tyr Val Asp Trp Ser Leu Val Asp
        595                 600                 605

Val Leu Arg Gly Ala Glu Asn Ser Pro Pro Leu Asp Arg Val Asp Val
    610                 615                 620

Leu Gln Pro Ala Ser Phe Ala Val Met Val Ser Leu Ala Glu Val Trp
625                 630                 635                 640

Arg Ser Tyr Gly Val Arg Pro Ala Ala Val Val Gly His Ser Gln Gly
                645                 650                 655

Glu Ile Ala Ala Ala Cys Ala Ala Gly Val Leu Pro Leu Glu Asp Ala
            660                 665                 670

Ala Arg Leu Val Ala Leu Arg Ser Arg Ala Leu Lys Gly Leu Ser Gly
        675                 680                 685

Arg Gly Gly Met Ala Ser Leu Ala Cys Pro Ala Asp Glu Val Ala Ala
    690                 695                 700

Leu Phe Ala Gly Ser Gly Gly Arg Leu Glu Val Ala Ala Ile Asn Gly
705                 710                 715                 720

Pro Arg Ser Val Val Val Ser Gly Asp Leu Glu Ala Val Asp Glu Leu
                725                 730                 735

Leu Ala Glu Cys Ala Glu Lys Asp Met Arg Ala Arg Arg Ile Pro Val
            740                 745                 750

Asp Tyr Ala Ser His Ser Ala His Val Glu Val Val Arg Ser Pro Val
        755                 760                 765

Leu Ala Ala Ala Ala Gly Val Arg His Arg Asp Gly Gln Val Pro Trp
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BNSDOCID: <WO___9946387A1_I_>

770 775 780

Trp Ser Thr Val Ile Gly Asp Trp Val Asp Pro Ala Arg Leu Asp Gly
785 790 795 800

Glu Tyr Trp Tyr Arg Asn Leu Arg Gln Pro Val Arg Phe Glu His Ala
805 810 815

Val Gln Gly Leu Val Glu Arg Gly Phe Gly Leu Phe Ile Glu Met Ser
820 825 830

Ala His Pro Val Leu Thr Thr Ala Val Glu Glu Thr Gly Ala Glu Ser
835 840 845

Glu Thr Ala Val Ala Ala Val Gly Thr Leu Arg Arg Asp Ser Gly Gly
850 855 860

Leu Arg Arg Leu Leu His Ser Leu Ala Glu Ala Tyr Val Arg Gly Ala
865 870 875 880

Thr Val Asp Trp Ala Val Ala Phe Gly Gly Ala Gly Arg Arg Leu Asp
885 890 895

Leu Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Asp Lys Gly
900 905 910

Ala Ala Ser Asp Glu Ala Arg Ala Val Ser Asp Pro Ala Ala Gly Trp
915 920 925

Phe Trp Gln Ala Val Ala Arg Gln Asp Leu Lys Ser Val Ser Asp Ala
930 935 940

Leu Asp Leu Asp Ala Asp Ala Pro Leu Ser Ala Thr Leu Pro Ala Leu
945 950 955 960

Ser Val Trp His Arg Gln Glu Arg Glu Arg Val Leu Ala Asp Gly Trp
965 970 975

Arg Tyr Arg Val Asp Trp Val Arg Val Ala Pro Gln Pro Val Arg Arg
980 985 990

Thr Arg Glu Thr Trp Leu Leu Val Val Pro Pro Gly Gly Ile Glu Glu
995 1000 1005

Ala Leu Val Glu Arg Leu Thr Asp Ala Leu Asn Thr Arg Gly Ile Ser
1010 1015 1020

Thr Leu Arg Leu Asp Val Pro Pro Ala Ala Thr Ser Gly Glu Leu Ala
1025 1030 1035 1040

Thr Glu Leu Arg Ala Ala Ala Asp Gly Asp Pro Val Lys Ala Ile Leu
1045 1050 1055

Ser Leu Thr Ala Leu Asp Glu Arg Pro His Pro Glu Cys Lys Asp Val
1060 1065 1070

Pro Ser Gly Ile Ala Leu Leu Leu Asn Leu Val Lys Ala Leu Gly Glu
1075 1080 1085

BNSDOCID: <WO___9946387A1_I_>

Ala Asp Leu Arg Ile Pro Leu Trp Thr Ile Thr Arg Gly Ala Val Lys
1090 1095 1100

Ala Gly Pro Ala Asp Arg Leu Leu Arg Pro Met Gln Ala Gln Ala Trp
1105 1110 1115 1120

Gly Leu Gly Arg Val Ala Ala Leu Glu His Pro Glu Arg Trp Gly Gly
1125 1130 1135

Leu Ile Asp Leu Pro Asp Ser Leu Asp Gly Asp Val Leu Thr Arg Leu
1140 1145 1150

Gly Glu Ala Leu Thr Asn Gly Leu Ala Glu Asp Gln Leu Ala Ile Arg
1155 1160 1165

Gln Ser Gly Val Leu Ala Arg Arg Leu Val Pro Ala Pro Ala Asn Gln
1170 1175 1180

Pro Ala Gly Arg Lys Trp Arg Pro Arg Gly Ser Ala Leu Ile Thr Gly
1185 1190 1195 1200

Gly Leu Gly Ala Val Gly Ala Gln Val Ala Arg Trp Leu Ala Glu Ile
1205 1210 1215

Gly Ala Glu Arg Ile Val Leu Thr Ser Arg Arg Gly Asn Gln Ala Ala
1220 1225 1230

Gly Ala Ala Glu Leu Glu Ala Glu Leu Arg Ala Leu Gly Ala Gln Val
1235 1240 1245

Ser Ile Val Ala Cys Asp Val Thr Asp Arg Ala Glu Met Ser Ala Leu
1250 1255 1260

Leu Ala Glu Phe Asp Val Thr Ala Val Phe His Ala Ala Gly Val Gly
1265 1270 1275 1280

Arg Leu Leu Pro Leu Ala Glu Thr Asp Gln Asn Gly Leu Ala Glu Ile
1285 1290 1295

Cys Ala Ala Lys Val Arg Gly Ala Gln Val Leu Asp Glu Leu Cys Asp
1300 1305 1310

Ser Thr Asp Leu Asp Ala Phe Val Leu Phe Ser Ser Gly Ala Gly Val
1315 1320 1325

Trp Gly Gly Gly Gly Gln Gly Ala Tyr Gly Ala Ala Asn Ala Phe Leu
1330 1335 1340

Asp Thr Leu Ala Glu Gln Arg Arg Ala Arg Gly Leu Pro Ala Thr Ser
1345 1350 1355 1360

Ile Ser Trp Gly Ser Trp Ala Gly Gly Gly Met Ala Asp Gly Ala Ala
1365 1370 1375

Gly Glu His Leu Arg Arg Arg Gly Ile Arg Pro Met Pro Ala Ala Ser
1380 1385 1390

BNSDOCID: <WO___9946387A1_I_>

Ala Ile Leu Ala Leu Gln Glu Val Leu Asp Gln Asp Glu Thr Cys Val
1395 1400 1405

Ser Ile Ala Asp Val Asp Trp Asp Arg Phe Val Pro Thr Phe Ala Ala
1410 1415 1420

Thr Arg Ala Thr Arg Leu Phe Asp Glu Val Pro Ala Ala Arg Lys Ala
1425 1430 1435 1440

Met Pro Ala Asn Gly Pro Ala Glu Pro Gly Gly Ser Pro Phe Ala Arg
1445 1450 1455

Asn Leu Ala Glu Leu Pro Glu Ala Gln Arg Arg His Glu Leu Val Asp
1460 1465 1470

Leu Val Cys Ala Gln Val Ala Thr Val Leu Gly His Gly Ser Arg Glu
1475 1480 1485

Glu Val Gln Pro Glu Arg Ala Phe Arg Ala Leu Gly Phe Asp Ser Leu
1490 1495 1500

Met Ala Val Asp Leu Arg Asn Arg Leu Thr Thr Ala Thr Gly Leu Arg
1505 1510 1515 1520

Leu Pro Thr Thr Thr Val Phe Asp Tyr Pro Asn Pro Ala Ala Leu Ala
1525 1530 1535

Ala His Leu Leu Glu Glu Leu Val Gly Asp Val Ala Ser Ala Ala Val
1540 1545 1550

Thr Ala Ala Ser Ala Pro Ala Ser Asp Glu Pro Ile Ala Ile Val Ala
1555 1560 1565

Met Ser Cys Arg Phe Pro Gly Gly Ala His Ser Pro Glu Asp Leu Trp
1570 1575 1580

Arg Leu Val Ala Ala Gly Thr Glu Val Ile Gly Glu Phe Pro Ser Asp
1585 1590 1595 1600

Arg Gly Trp Asp Ala Glu Gly Leu Tyr Asp Pro Asp Ala Ser Arg Pro
1605 1610 1615

Gly Thr Thr Tyr Ala Arg Met Ala Gly Phe Leu Tyr Asp Ala Gly Glu
1620 1625 1630

Phe Asp Ala Asp Leu Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met
1635 1640 1645

Asp Pro Gln Gln Arg Leu Val Leu Glu Ile Ala Trp Glu Ala Leu Glu
1650 1655 1660

Arg Ala Gly Ile Asp Pro Leu Ser Leu Lys Gly Ser Gly Val Gly Thr
1665 1670 1675 1680

Tyr Ile Gly Ala Gly Ser Arg Gly Tyr Ala Thr Asp Val Arg Gln Phe
1685 1690 1695

Pro Glu Glu Ala Glu Gly Tyr Leu Leu Thr Gly Thr Ser Ala Ser Val

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1700 1705 1710

Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val
1715 1720 1725

Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala
1730 1735 1740

Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly
1745 1750 1755 1760

Val Thr Val Met Ser Thr Pro Glu Met Phe Val Glu Phe Ser Arg Gln
1765 1770 1775

Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala
1780 1785 1790

Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Leu Leu Leu Glu Arg
1795 1800 1805

Leu Ser Asp Ala His Arg Asn Gly His Arg Val Leu Ala Val Val Arg
1810 1815 1820

Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Ala Ala Pro
1825 1830 1835 1840

Asn Gly Pro Ser Gln Gln Arg Val Ile Asn Gln Ala Leu Ala Asn Ala
1845 1850 1855

Ala Leu Ser Ala Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly
1860 1865 1870

Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr
1875 1880 1885

Gly Gln Ala Arg Glu Arg Asp Arg Pro Leu Trp Leu Gly Ser Val Lys
1890 1895 1900

Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile
1905 1910 1915 1920

Lys Met Val Met Ala Met Arg His Gly Gln Leu Pro Ala Ser Leu His
1925 1930 1935

Ala Asp Glu Pro Thr Ser Glu Val Asp Trp Ser Ser Gly Ala Val Arg
1940 1945 1950

Leu Leu Ala Glu Gln Val Pro Trp Pro Glu Ser Asp Arg Val Arg Arg
1955 1960 1965

Val Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile
1970 1975 1980

Leu Glu Gln Ala Thr Asn Ala Pro Asp Ser Thr Ala Glu Thr Asp Lys
1985 1990 1995 2000

Thr Glu Ser Gly Ser Thr Val Asp Ile Pro Val Val Pro Trp Leu Val
2005 2010 2015

BNSDOCID: <WO___9946387A1_I_>

Ser Gly Lys Thr Thr Asp Ser Leu Arg Gly Gln Ala Glu Arg Val Leu
2020 2025 2030

Ser Gln Val Glu Ser Arg Pro Glu Gln Arg Ser Leu Asp Val Ala Tyr
2035 2040 2045

Ser Leu Ala Ser Gly Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu
2050 2055 2060

Gly Ala Asp Arg Gly Glu Leu Val Ala Gly Leu Ala Ala Leu Ala Ala
2065 2070 2075 2080

Gly Gln Glu Ala Ser Gly Val Ile Ser Gly Thr Arg Ala Ser Ala Arg
2085 2090 2095

Phe Gly Phe Val Phe Ser Gly Gln Gly Gly Gln Trp Leu Gly Met Gly
2100 2105 2110

Arg Ala Leu Tyr Ser Lys Phe Pro Val Phe Ala Ala Ala Phe Asp Glu
2115 2120 2125

Ala Cys Ala Glu Leu Glu Ala His Leu Gly Glu Asp Arg Arg Val Arg
2130 2135 2140

Asp Val Val Phe Gly Ser Asp Ala Gln Leu Leu Asp Gln Thr Leu Trp
2145 2150 2155 2160

Ala Gln Ser Gly Leu Phe Ala Leu Gln Ala Gly Leu Leu Gly Leu Leu
2165 2170 2175

Gly Ser Trp Gly Val Arg Pro Asp Val Val Met Gly His Ser Val Gly
2180 2185 2190

Glu Leu Ala Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala
2195 2200 2205

Ala Arg Leu Val Ala Ala Arg Ala Arg Leu Met Gln Ala Leu Pro Ser
2210 2215 2220

Asp Gly Ala Met Leu Ala Val Ala Ala Gly Glu Asp Leu Val Arg Pro
2225 2230 2235 2240

Leu Leu Ala Gly Arg Glu Glu Ser Val Ser Val Ala Ala Leu Asn Ala
2245 2250 2255

Pro Gly Ser Val Val Leu Ser Gly Asp Arg Glu Val Leu Ala Ser Ile
2260 2265 2270

Val Gly Arg Leu Thr Glu Leu Arg Val Arg Thr Arg Arg Leu Arg Val
2275 2280 2285

Ser His Ala Phe His Ser His Arg Met Asp Pro Met Leu Gly Glu Phe
2290 2295 2300

Ala Gln Ile Ala Glu Ser Ala Glu Phe Gly Lys Pro Thr Thr Pro Leu
2305 2310 2315 2320

BNSDOCID: <WO___9946387A1_I_>

Val Ser Thr Leu Thr Gly Glu Leu Asp Arg Ala Ala Glu Met Ser Thr
2325 2330 2335

Pro Gly Tyr Trp Val Arg Gln Ala Arg Glu Pro Val Arg Phe Ala Asp
2340 2345 2350

Gly Val Gln Ala Leu Ala Ala Gln Gly Ile Gly Thr Val Val Glu Leu
2355 2360 2365

Gly Pro Asp Gly Thr Leu Ala Ala Leu Val Arg Glu Cys Ala Thr Glu
2370 2375 2380

Ser Asp Arg Val Gly Arg Ile Ser Ser Ile Pro Leu Met Arg Arg Glu
2385 2390 2395 2400

Arg Asp Glu Thr Arg Ser Val Met Thr Ala Leu Ala His Leu His Thr
2405 2410 2415

Arg Gly Gly Glu Val Asp Trp Gln Ala Phe Phe Ala Gly Thr Gly Ala
2420 2425 2430

Arg Gln Leu Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln His Tyr Trp
2435 2440 2445

Ile Glu Ser Ser Ala Arg Pro Ala Arg Asp Arg Ala Asp Ile Gly Glu
2450 2455 2460

Val Ala Glu Gln Phe Trp Thr Ala Val Asp Gln Gly Asp Leu Ala Thr
2465 2470 2475 2480

Leu Val Ala Ala Leu Asp Leu Gly Ala Asp Asp Asp Thr Cys Ala Ser
2485 2490 2495

Leu Ser Asp Val Leu Pro Ala Leu Ser Ser Trp Arg Ser Gly Leu Arg
2500 2505 2510

Asn Arg Ser Leu Val Asp Ser Cys Arg Tyr Arg Ile Ser Trp His Ser
2515 2520 2525

Ser Arg Glu Val Pro Ala Pro Lys Ile Ser Gly Thr Trp Leu Leu Val
2530 2535 2540

Val Pro Gly Ala Ala Asp Asp Gly Leu Val Thr Ala Leu Thr Ser Ser
2545 2550 2555 2560

Leu Val Gly Gly Gly Ala Glu Val Val Arg Ile Gly Leu Ser Glu Glu
2565 2570 2575

Asp Pro His Arg Glu Asp Val Ala Gln Arg Leu Ala Asn Ala Leu Thr
2580 2585 2590

Asp Ala Gly Gln Leu Gly Gly Val Leu Ser Leu Leu Gly Leu Asp Glu
2595 2600 2605

Ser Pro Ala Pro Gly Phe Ser Cys Leu Pro Thr Gly Phe Ala Leu Thr
2610 2615 2620

Val Gln Leu Leu Arg Ala Leu Arg Lys Ala Asp Val Glu Ala Pro Phe

BNSDOCID: <WO___9946387A1_I_>

2625 2630 2635 2640

Trp Ala Val Thr Arg Gly Gly Val Ala Leu Glu Asp Val Arg Val Ser
2645 2650 2655

Pro Glu Gln Ala Leu Val Trp Gly Leu Leu Arg Val Ala Gly Leu Glu
2660 2665 2670

His Pro Glu Phe Trp Gly Gly Leu Ile Asp Leu Pro Ser Asp Trp Asp
2675 2680 2685

Asp Arg Leu Gly Ala Arg Leu Ala Gly Val Leu Ala Asp Gly Gly Glu
2690 2695 2700

Asp Gln Val Ala Ile Arg Arg Gly Gly Val Phe Val Arg Arg Leu Glu
2705 2710 2715 2720

Arg Ala Gly Ala Ser Gly Ala Gly Ser Val Trp Arg Pro Arg Gly Thr
2725 2730 2735

Val Leu Val Thr Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala Arg
2740 2745 2750

Trp Leu Ala Gly Ala Gly Ala Glu His Val Val Leu Thr Ser Arg Arg
2755 2760 2765

Gly Ala Asp Ala Pro Gly Ala Gly Glu Leu Arg Ala Glu Leu Glu Ala
2770 2775 2780

Leu Gly Ala Arg Val Ser Ile Val Pro Cys Asp Val Ala Asp Arg Asp
2785 2790 2795 2800

Ala Val Ala Gly Val Leu Ala Gly Ile Gly Gly Glu Cys Pro Leu Thr
2805 2810 2815

Ala Val Val His Ala Ala Gly Val Gly Glu Ala Gly Asp Val Val Glu
2820 2825 2830

Met Gly Leu Ala Asp Phe Ala Ala Val Leu Ser Ala Lys Val Arg Gly
2835 2840 2845

Ala Ala Asn Leu Asp Glu Leu Leu Ala Asp Ser Glu Leu Asp Ala Phe
2850 2855 2860

Val Met Phe Ser Ser Val Ser Gly Val Trp Gly Ala Gly Gly Gln Gly
2865 2870 2875 2880

Ala Tyr Ala Ala Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Gln Arg
2885 2890 2895

Arg Ala Arg Gly Leu Val Gly Thr Ala Val Ala Trp Gly Pro Trp Ala
2900 2905 2910

Gly Asp Gly Met Ala Ala Gly Glu Thr Gly Ala Gln Leu His Arg Met
2915 2920 2925

Gly Leu Ala Ser Met Glu Pro Ser Ala Ala Leu Leu Ala Leu Gln Gly
2930 2935 2940

BNSDOCID: <WO___9946387A1_I_>

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Ala Leu Asp Arg Asp Glu Thr Ser Leu Val Val Ala Asp Val Asp Trp
2945                2950                2955                2960

Ala Arg Phe Ala Pro Ala Phe Thr Ser Ala Arg Arg Arg Pro Leu Leu
                2965                2970                2975

Asp Thr Ile Asp Glu Ala Arg Ala Ala Leu Glu Thr Thr Gly Glu Gln
            2980                2985                2990

Ala Gly Thr Gly Lys Pro Val Glu Leu Thr Gln Arg Leu Ala Gly Leu
        2995                3000                3005

Ser Arg Lys Glu Arg Asp Asp Ala Val Leu Asp Leu Val Arg Ala Glu
    3010                3015                3020

Thr Ala Ala Val Leu Gly Arg Asp Asp Ala Thr Ala Leu Ala Pro Ser
3025                3030                3035                3040

Arg Pro Phe Gln Glu Leu Gly Phe Asp Ser Leu Met Ala Val Glu Leu
                3045                3050                3055

Arg Asn Arg Leu Asn Thr Ala Thr Gly Ile Gln Leu Pro Ala Ser Thr
            3060                3065                3070

Ile Phe Asp Tyr Pro Asn Ala Glu Ser Leu Ser Arg His Leu Cys Ala
        3075                3080                3085

Glu Leu Phe Pro Thr Glu Thr Thr Val Asp Ser Ala Leu Ala Glu Leu
    3090                3095                3100

Asp Arg Ile Glu Gln Gln Leu Ser Met Leu Thr Gly Glu Ala Arg Ala
3105                3110                3115                3120

Arg Asp Arg Ile Ala Thr Arg Leu Arg Ala Leu His Glu Lys Trp Asn
                3125                3130                3135

Ser Ala Ala Glu Val Pro Thr Gly Ala Asp Val Leu Ser Thr Leu Asp
            3140                3145                3150

Ser Ala Thr His Asp Glu Ile Phe Glu Phe Ile Asp Asn Glu Leu Asp
        3155                3160                3165

Leu Ser
    3170
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<210> 5
<211> 4928
<212> PRT
<213> Saccharopolyspora spinosa

<400> 5

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Val Glu Ile Thr Met Ala Asn Glu Glu Lys Leu Phe Gly Tyr Leu Lys
  1               5                  10                  15

Lys Val Thr Ala Asp Leu His Gln Thr Arg Gln Arg Leu Leu Ala Ala
             20                  25                  30
```


BNSDOCID: <WO___9946387A1_I_>

Glu Ser Arg Ser Gln Glu Pro Ile Ala Ile Val Ser Ala Ser Cys Arg
35 40 45

Leu Pro Gly Gly Val Asp Ser Pro Glu Ala Leu Trp Gln Leu Val Arg
50 55 60

Thr Gly Thr Asp Ala Ile Ser Glu Phe Pro Ala Asp Arg Gly Trp Asp
65 70 75 80

Leu Gly Arg Leu Tyr Asp Pro Asp Pro Asn His Gln Gly Thr Ser Tyr
85 90 95

Thr Arg Ala Gly Gly Phe Leu Ala Gly Ala Gly Asp Phe Asp Pro Ala
100 105 110

Met Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
115 120 125

Arg Leu Leu Leu Glu Leu Ser Trp Glu Ala Leu Glu Arg Ala Gly Ile
130 135 140

Asp Pro Thr Ser Leu Arg Gly Ser Lys Thr Gly Val Phe Gly Gly Val
145 150 155 160

Thr Pro Gln Glu Tyr Gly Pro Ser Leu Gln Glu Met Ser Arg Asn Ala
165 170 175

Gly Gly Phe Gly Leu Thr Gly Arg Met Val Ser Val Ala Ser Gly Arg
180 185 190

Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr
195 200 205

Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu
210 215 220

Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met
225 230 235 240

Ala Thr Pro Ala Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
245 250 255

Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr Gly
260 265 270

Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
275 280 285

Arg Arg Asn Gly His Glu Val Leu Ala Val Val Arg Gly Ser Ala Val
290 295 300

Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
305 310 315 320

Gln Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser Val
325 330 335

BNSDOCID: <WO___9946387A1_I_>

```
Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Thr Leu Gly
            340                 345                 350

Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly Arg
        355                 360                 365

Glu Lys Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly
    370                 375                 380

His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Leu
385                 390                 395                 400

Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu Pro
                405                 410                 415

Thr Ser Ala Val Asp Trp Ser Ala Gly Ser Val Arg Leu Leu Thr Glu
            420                 425                 430

Asn Thr Pro Trp Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser
        435                 440                 445

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser
    450                 455                 460

Pro Val Glu Gln Gly Glu Pro Ala Gly Pro Val Glu Gly Glu Arg Glu
465                 470                 475                 480

Pro Asp Val Ala Val Pro Val Val Pro Trp Val Leu Ser Gly Lys Thr
                485                 490                 495

Pro Glu Ala Ala Arg Ala Gln Ala Glu Arg Val His Ser His Ile Glu
            500                 505                 510

Asp Arg Pro Gly Leu Ser Pro Val Asp Val Ala Tyr Ser Leu Gly Met
        515                 520                 525

Thr Arg Ala Ala Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg
    530                 535                 540

Ala Ala Leu Leu Thr Gly Leu Arg Ala Phe Ala Asp Gly Cys Asp Ala
545                 550                 555                 560

Pro Glu Val Val Ser Gly Ser Val Gly Leu Gly Gly Arg Val Gly Phe
                565                 570                 575

Val Phe Ser Gly Gln Gly Gly Gln Trp Pro Gly Met Gly Arg Gly Leu
            580                 585                 590

Tyr Ser Val Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala
        595                 600                 605

Glu Leu Asp Ala His Leu Gly Gln Glu Leu Arg Val Arg Asp Val Val
    610                 615                 620

Phe Gly Ser Gln Ala Trp Leu Leu Asp Arg Thr Val Trp Ala Gln Ser
625                 630                 635                 640

Gly Leu Phe Ala Leu Gln Ile Gly Leu Leu Arg Leu Leu Gly Ser Trp
```


BNSDOCID: <WO___9946387A1_I_>

645 650 655

Gly Val Arg Pro Asp Val Val Leu Gly His Ser Val Gly Glu Leu Ala
660 665 670

Ala Val His Ala Ala Gly Val Leu Ser Leu Ser Glu Ala Ala Arg Leu
675 680 685

Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala
690 695 700

Met Leu Ala Val Ala Thr Gly Glu Phe Gln Val Asp Pro Leu Leu Asp
705 710 715 720

Gly Val Arg Asp Arg Ile Gly Ile Ala Ala Val Asn Gly Pro Glu Ser
725 730 735

Val Val Leu Ser Gly Asp Arg Glu Leu Leu Thr Glu Ile Ala Asp Arg
740 745 750

Leu His Asp Gln Gly Cys Arg Thr Arg Trp Leu Arg Val Ser His Ala
755 760 765

Phe His Ser Pro His Met Glu Pro Met Leu Glu Glu Phe Ala Gln Ile
770 775 780

Ser Arg Gly Arg Glu Tyr His Ala Pro Glu Leu Pro Ile Ile Ser Thr
785 790 795 800

Leu Ile Gly Glu Leu Asp Gly Gly Arg Val Met Gly Thr Pro Glu Tyr
805 810 815

Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Glu Gly Val Gln
820 825 830

Ala Leu Val Gly Gln Gly Val Gly Thr Ile Val Glu Leu Gly Pro Asp
835 840 845

Gly Ala Leu Ser Thr Leu Val Glu Glu Cys Val Ala Glu Ser Gly Arg
850 855 860

Val Ala Gly Ile Pro Leu Met Arg Lys Asp Arg Asp Glu Ala Arg Thr
865 870 875 880

Val Leu Ala Ala Leu Ala Gln Ile His Thr Arg Gly Gly Glu Val Asp
885 890 895

Trp Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Val Asp Leu Pro
900 905 910

Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Ala Ser Thr Gly Arg
915 920 925

Ala Gly Asp Val Thr Ala Ala Gly Leu Ala Glu Ala Asp His Pro Leu
930 935 940

Leu Gly Ala Val Val Ala Leu Ala Asp Gly Glu Gly Val Val Leu Thr
945 950 955 960

BNSDOCID: <WO___9946387A1_I_>

```
Gly Arg Leu Thr Ala Gly Ser His Pro Trp Leu Ser Asp His Arg Val
                965                 970                 975

Leu Gly Glu Ile Val Val Pro Gly Thr Ala Ile Val Glu Leu Val Trp
            980                 985                 990

His Val Gly Glu Arg Leu Gly Cys Gly Arg Val Glu Glu Leu Ala Leu
        995                1000                1005

Glu Ala Pro Leu Ile Leu Pro Asp His Gly Ala Val Gln Val Gln Val
   1010                1015                1020

Leu Val Gly Pro Pro Gly Glu Ser Gly Ala Arg Ser Val Ala Leu Tyr
1025                1030                1035                1040

Ser Cys Pro Gly Glu Ala Ile Glu Pro Glu Trp Lys Lys His Ala Thr
                1045                1050                1055

Gly Val Leu Leu Pro Pro Val Ala Ala Glu Asn His Glu Leu Thr Ala
            1060                1065                1070

Trp Pro Pro Glu Asn Ala Thr Glu Ile Asp Ala Asp Gly Val Tyr Ala
        1075                1080                1085

Phe Leu Glu Gly His Gly Phe Ala Tyr Gly Pro Ala Phe Arg Cys Leu
   1090                1095                1100

Arg Gly Ala Trp Arg Arg Gly Gly Glu Val Phe Ala Glu Val Ala Leu
1105                1110                1115                1120

Pro Asp Asp Met Gln Ala Gly Val Asp Arg Phe Gly Val His Pro Ala
                1125                1130                1135

Leu Leu Asp Ala Val Leu His Ala Ala Ala Ala Glu Thr Ser Val Val
            1140                1145                1150

Gln Ser Glu Ala Arg Val Pro Phe Ser Trp Arg Gly Val Glu Leu Arg
        1155                1160                1165

Ala Thr Glu Ser Ala Val Val Arg Ala Arg Leu Ser Leu Thr Ser Asp
   1170                1175                1180

Asp Glu Leu Ser Leu Val Ala Val Asp Pro Ala Gly Arg Phe Val Ala
1185                1190                1195                1200

Thr Val Asp Ser Leu Val Thr Arg Pro Ile Ser Arg Gln Gln Val Arg
                1205                1210                1215

Ser Gly Ala Ile Gly Asp Cys Leu Phe Glu Val Glu Trp His Arg Lys
            1220                1225                1230

Ala Leu Leu Gly Thr Thr Ala Gly Asp Asp Leu Ala Ile Val Gly Asp
        1235                1240                1245

Gly Pro Ser Trp Pro Glu Ser Val Arg Ala Thr Ala Arg Phe Ala Thr
   1250                1255                1260
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BNSDOCID: <WO___9946387A1_I_>

Leu Asp Glu Phe Arg Ala Ala Val Asp Ser Asp Val Pro Ala Pro Gly
1265 1270 1275 1280

Ser Val Leu Val Ala Ala Met Ser Ala Glu Glu Val Glu Gly Gly Ser
1285 1290 1295

Leu Pro Ser Arg Ala Gln Glu Ser Thr Ser Asp Leu Leu Ala Leu Val
1300 1305 1310

Gln Ser Trp Leu Ala Asp Glu Arg Phe Ala Glu Ser Gln Leu Val Val
1315 1320 1325

Val Thr Arg Ala Ala Val Ser Ala Asp Ser Asp Ser Asp Val Ala Asp
1330 1335 1340

Leu Val Gly Ala Ser Ser Trp Gly Leu Leu Ser Ser Ala Gln Ser Glu
1345 1350 1355 1360

Asn Pro Gly Arg Phe Val Leu Val Asp Val Asp Gly Thr Pro Glu Ser
1365 1370 1375

Trp Gln Ala Leu Pro Ala Ala Val Arg Ala Gly Glu Pro Gln Leu Ala
1380 1385 1390

Leu Arg Arg Gly Val Ala Leu Val Pro Arg Leu Ala Arg Leu Thr Val
1395 1400 1405

Arg Glu Glu Gly Ser Ser Pro Gln Leu Asp Thr Asp Gly Thr Val Leu
1410 1415 1420

Ile Thr Gly Gly Thr Gly Ala Leu Gly Gly Val Val Ala Arg His Leu
1425 1430 1435 1440

Val Glu Glu His Gly Ile Arg Arg Leu Val Leu Ala Gly Arg Arg Gly
1445 1450 1455

Trp Asn Ala Pro Gly Val His Glu Leu Val Asp Glu Leu Ala Arg Ala
1460 1465 1470

Gly Ala Val Val Glu Val Val Ala Cys Asp Val Ala Asp Arg Thr Asp
1475 1480 1485

Leu Glu His Val Leu Ala Ala Ile Pro Val Asp Trp Pro Leu Arg Gly
1490 1495 1500

Ile Val His Thr Ala Gly Val Leu Ala Asp Gly Val Ile Gly Ser Leu
1505 1510 1515 1520

Ser Ala Ala Asp Val Gly Thr Val Phe Ala Pro Lys Val Thr Gly Ala
1525 1530 1535

Trp His Leu His Glu Leu Thr Arg Asp Leu Asp Leu Ser Phe Phe Val
1540 1545 1550

Leu Phe Ser Ser Phe Ser Gly Ile Ala Gly Ala Ala Gly Gln Ala Asn
1555 1560 1565

Tyr Ala Ala Ala Asn Thr Phe Leu Asp Ala Leu Ala Arg Tyr Arg Arg

BNSDOCID: <WO___9946387A1_I_>

```
   1570                1575                1580

Ala Arg Gly Leu Pro Gly Leu Ser Leu Ala Trp Gly Leu Trp Ala Gln
1585                1590                1595                1600

Pro Ser Gly Met Thr Ser Gly Leu Asp Ala Ala Ser Val Glu Arg Leu
                1605                1610                1615

Ala Arg Thr Gly Ile Ala Glu Leu Ser Thr Glu Asp Gly Leu Arg Leu
            1620                1625                1630

Phe Asp Ala Ala Phe Ala Lys Asp Arg Ala Cys Val Val Ala Ala Arg
        1635                1640                1645

Leu Asp Arg Ala Leu Leu Val Gly Asn Gly Arg Ser His Ala Ile Pro
    1650                1655                1660

Ala Leu Leu Ser Ala Leu Val Pro Val Arg Gly Gly Val Ala Arg Lys
1665                1670                1675                1680

Thr Ala Asn Ser Gln Ala Ala Asp Glu Asp Ala Leu Leu Gly Leu Val
                1685                1690                1695

Arg Glu His Val Ser Ala Val Leu Gly Tyr Ser Gly Ala Val Glu Val
            1700                1705                1710

Gly Gly Asp Arg Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly
        1715                1720                1725

Val Glu Leu Arg Asn Arg Leu Ala Gly Val Leu Gly Val Arg Leu Pro
    1730                1735                1740

Ala Thr Ala Val Phe Asp Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe
1745                1750                1755                1760

Leu His Gln Glu Leu Ala Gly Glu Val Ala Ser Thr Ser Thr Pro Val
                1765                1770                1775

Thr Arg Ala Ala Ser Ala Glu Glu Asp Leu Val Ala Ile Val Gly Met
            1780                1785                1790

Gly Cys Arg Phe Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg
        1795                1800                1805

Leu Val Ala Gly Gly Val Asp Ala Val Ala Gly Phe Pro Asp Asp Arg
    1810                1815                1820

Gly Trp Asp Leu Ala Ala Leu Tyr Asp Pro Asp Pro Asp Arg Leu Gly
1825                1830                1835                1840

Thr Ser Tyr Val Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe
                1845                1850                1855

Asp Ala Asp Met Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp
            1860                1865                1870

Pro Gln Gln Arg Leu Leu Leu Glu Val Ala Trp Glu Thr Leu Glu Arg
        1875                1880                1885
```


BNSDOCID: <WO___9946387A1_I_>

Ala Gly Ile Asp Pro Phe Ser Leu His Gly Ser Arg Thr Gly Val Phe
1890 1895 1900

Ala Gly Leu Met Tyr His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala
1905 1910 1915 1920

Pro Glu Gly Phe Glu Gly His Leu Gly Thr Gly Asn Ala Gly Ser Val
1925 1930 1935

Leu Ser Gly Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val
1940 1945 1950

Thr Val Asp Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala
1955 1960 1965

Gly Gln Ala Leu Arg Ala Gly Glu Cys Glu Phe Ala Leu Ala Gly Gly
1970 1975 1980

Val Thr Val Met Ser Thr Pro Thr Thr Phe Val Glu Phe Ser Arg Gln
1985 1990 1995 2000

Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala
2005 2010 2015

Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg
2020 2025 2030

Leu Ser Asp Ala Arg Arg Asn Gly His Glu Val Leu Ala Val Val Arg
2035 2040 2045

Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro
2050 2055 2060

Asn Gly Pro Ser Gln Gln Arg Val Ile Thr Gln Ala Leu Thr Ser Ala
2065 2070 2075 2080

Gly Leu Ser Val Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly
2085 2090 2095

Thr Arg Leu Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr
2100 2105 2110

Gly Arg Asp Arg Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys
2115 2120 2125

Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile
2130 2135 2140

Lys Met Val Met Ala Met Arg Gln Gly Glu Leu Pro Arg Thr Leu His
2145 2150 2155 2160

Val Asp Glu Pro Ser Ala Gln Val Asp Trp Ser Ala Gly Thr Val Gln
2165 2170 2175

Leu Leu Thr Glu Asn Thr Pro Trp Pro Asp Ser Gly Arg Leu Arg Arg
2180 2185 2190

BNSDOCID: <WO___9946387A1_I_>

```
Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Leu Ile
       2195                2200                2205

Leu Glu Gln Pro Pro Arg Glu Ser Gln Arg Ser Thr Glu Pro Asp Ser
   2210                2215                2220

Gly Ser Val Arg Asp Phe Pro Val Val Pro Trp Met Val Ser Gly Lys
2225                2230                2235                2240

Thr Pro Glu Ala Leu Ser Ala Gln Ala Asp Ala Leu Met Ser Tyr Leu
                2245                2250                2255

Ser Asn Arg Val Asp Ala Ser Pro Arg Asp Ile Gly Tyr Ser Leu Ala
           2260                2265                2270

Val Thr Arg Pro Ala Leu Asp His Arg Ala Val Val Leu Gly Ala Asp
       2275                2280                2285

Arg Ala Ala Leu Leu Pro Gly Leu Lys Ala Leu Ala Val Ser Asn Asp
   2290                2295                2300

Ala Ala Glu Val Ile Thr Gly Thr Arg Ala Ala Gly Pro Val Gly Phe
2305                2310                2315                2320

Val Phe Ser Gly Gln Gly Gly Gln Trp Pro Gly Met Gly Ser Gly Leu
                2325                2330                2335

His Ser Ala Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Cys
           2340                2345                2350

Glu Leu Asp Ala His Leu Gly Gln Met Ala Arg Leu Arg Asp Val Leu
       2355                2360                2365

Ser Gly Ser Asp Thr Gln Leu Leu Asp Gln Thr Leu Trp Ala Gln Pro
   2370                2375                2380

Gly Leu Phe Ala Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Ser Trp
2385                2390                2395                2400

Gly Val Arg Pro Ala Val Val Leu Gly His Ser Val Gly Glu Leu Ala
                2405                2410                2415

Ala Ala Phe Ala Ala Gly Val Leu Ser Leu Arg Asp Ala Ala Arg Leu
           2420                2425                2430

Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Thr Gly Gly Ala
       2435                2440                2445

Met Leu Ala Ala Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala
   2450                2455                2460

Asp Cys Gly Asp Arg Val Gly Ile Ala Ala Val Asn Ala Pro Gly Ser
2465                2470                2475                2480

Val Val Leu Ser Gly Asp Arg Asp Val Leu Asp Asp Ile Ala Gly Arg
                2485                2490                2495

Leu Asp Gly Gln Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala
```


BNSDOCID: <WO___9946387A1_I_>

2500 2505 2510

Phe His Ser His Arg Met Asp Pro Met Leu Ala Glu Phe Thr Glu Ile
2515 2520 2525

Ala Arg Ser Val Asp Tyr Arg Ser Ser Gly Leu Pro Ile Val Ser Thr
2530 2535 2540

Leu Thr Gly Glu Leu Asp Glu Val Gly Met Pro Ala Thr Pro Glu Tyr
2545 2550 2555 2560

Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Ala
2565 2570 2575

Ala Leu Ala Ala His Gly Val Ser Thr Val Val Glu Val Gly Pro Asp
2580 2585 2590

Gly Val Leu Ser Ala Leu Val Gln Glu Cys Ala Ala Gly Ser Asp Gln
2595 2600 2605

Gly Gly Arg Val Ala Ala Val Pro Leu Met Arg Ser Asn Arg Asp Glu
2610 2615 2620

Ala His Thr Val Thr Thr Ala Leu Ala Gln Ile His Val Arg Gly Ala
2625 2630 2635 2640

Glu Val Asp Trp Arg Ser Phe Phe Ala Gly Thr Gly Ala Lys Gln Val
2645 2650 2655

Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Asp Ser
2660 2665 2670

Pro Ser Glu Pro Val Gly Gln Ser Ala Asp Pro Ala Arg Gln Ser Gly
2675 2680 2685

Phe Trp Glu Leu Val Glu Gln Glu Asp Val Ser Ala Leu Ser Ala Ala
2690 2695 2700

Leu His Ile Thr Gly Asp His Asp Val Gln Ala Ser Leu Glu Ser Val
2705 2710 2715 2720

Val Pro Val Leu Ser Ser Trp His Arg Arg Ile Arg Asn Glu Ser Leu
2725 2730 2735

Val His Gln Trp Arg Tyr Arg Ile Ser Trp His Glu Arg Ala Asp Leu
2740 2745 2750

Pro Asp Pro Ser Leu Ser Gly Thr Trp Leu Val Val Val Pro Glu Gly
2755 2760 2765

Trp Ser Ala Ser Arg Gln Val Leu Arg Phe Asn Glu Met Phe Glu Glu
2770 2775 2780

Arg Gly Cys Pro Ala Val Leu Phe Glu Leu Ala Gly His Asp Glu Glu
2785 2790 2795 2800

Ala Leu Ala Gln Arg Phe Arg Ser Leu Pro Val Ala Ser Gly Gly Ile
2805 2810 2815

BNSDOCID: <WO___9946387A1_I_>

```
Ser Gly Val Leu Ser Leu Leu Ala Leu Asp Glu Ser Pro Ser Ser Pro
          2820                2825                2830

Asn Ala Ala Leu Pro Asn Gly Ala Leu Asn Ser Leu Val Leu Leu Arg
       2835                2840                2845

Ala Leu Arg Ala Ala Asp Val Ser Ala Pro Leu Trp Leu Ala Thr Cys
   2850                2855                2860

Gly Gly Val Ala Val Gly Asp Val Pro Val Asn Pro Gly Gln Ala Leu
2865                2870                2875                2880

Val Trp Gly Leu Gly Arg Val Val Gly Leu Glu His Pro Ala Trp Trp
               2885                2890                2895

Gly Gly Leu Val Asp Val Pro Cys Leu Leu Asp Glu Asp Ala Arg Glu
          2900                2905                2910

Arg Leu Ser Val Val Leu Ala Gly Leu Gly Glu Asp Glu Ile Ala Val
       2915                2920                2925

Arg Pro Gly Gly Val Phe Val Arg Arg Leu Glu Arg Ala Gly Ala Ala
   2930                2935                2940

Ser Gly Ala Gly Ser Val Trp Arg Pro Arg Gly Thr Val Leu Val Thr
2945                2950                2955                2960

Gly Gly Thr Gly Gly Leu Gly Ala His Val Ala Arg Trp Leu Ala Gly
               2965                2970                2975

Ala Gly Ala Glu His Val Val Leu Thr Ser Arg Arg Gly Ala Ala Ala
          2980                2985                2990

Pro Gly Ala Gly Asp Leu Arg Ala Glu Leu Glu Ala Leu Gly Ala Arg
       2995                3000                3005

Val Ser Ile Thr Ala Cys Asp Val Ala Asp Arg Asp Ala Leu Ala Glu
   3010                3015                3020

Val Leu Ala Thr Ile Pro Asp Asp Cys Pro Leu Thr Ala Val Met His
3025                3030                3035                3040

Ala Ala Gly Val Val Glu Val Gly Asp Val Ala Ser Met Cys Leu Thr
               3045                3050                3055

Asp Phe Val Gly Val Leu Ser Ala Lys Ala Gly Gly Ala Ala Asn Leu
          3060                3065                3070

Asp Glu Leu Leu Ala Asp Val Glu Leu Asp Ala Phe Val Leu Phe Ser
       3075                3080                3085

Ser Val Ser Gly Val Trp Gly Ala Gly Gly Gln Gly Ala Tyr Ala Ala
   3090                3095                3100

Ala Asn Ala Tyr Leu Asp Ala Leu Ala Gln Gln Arg Arg Ala Arg Gly
3105                3110                3115                3120
```


BNSDOCID: <WO___9946387A1_I_>

Leu Val Gly Thr Ala Val Ala Trp Gly Pro Trp Ala Gly Asp Gly Met
3125 3130 3135

Ala Ala Gly Glu Gly Gly Ala Gln Leu Arg Arg Ala Gly Leu Val Pro
3140 3145 3150

Met Ala Ala Asp Arg Ala Leu Leu Ala Leu Gln Gly Ala Leu Asp Arg
3155 3160 3165

Asp Glu Thr Ser Leu Val Val Ala Asp Met Ala Trp Glu Arg Phe Ala
3170 3175 3180

Pro Val Phe Ala Met Ser Arg Arg Arg Pro Leu Leu Asp Glu Leu Pro
3185 3190 3195 3200

Glu Ala Gln Gln Ala Leu Ala Asp Ala Glu Asn Thr Thr Asp Ala Ala
3205 3210 3215

Asp Ser Ala Val Pro Leu Pro Arg Leu Ala Gly Met Ala Ala Ala Glu
3220 3225 3230

Arg Arg Arg Ala Met Leu Asp Leu Val Leu Ala Glu Ala Ser Ile Val
3235 3240 3245

Leu Gly His Asn Gly Ser Asp Pro Val Gly Pro Asp Arg Ala Phe Gln
3250 3255 3260

Glu Leu Gly Phe Asp Ser Leu Met Ala Val Glu Leu Arg Asn Arg Leu
3265 3270 3275 3280

Gly Glu Ala Thr Gly Leu Ser Leu Pro Ala Thr Leu Ile Phe Asp Tyr
3285 3290 3295

Pro Ser Pro Ser Ala Leu Ala Glu Gln Leu Val Gly Glu Leu Val Gly
3300 3305 3310

Ala Gln Pro Ala Thr Thr Val Val Ala Gly Ala Asp Pro Val Asp Asp
3315 3320 3325

Pro Val Val Val Val Ala Met Gly Cys Arg Tyr Pro Gly Asp Val Cys
3330 3335 3340

Ser Pro Glu Glu Leu Trp Gln Leu Val Ser Ala Gly Arg Asp Ala Val
3345 3350 3355 3360

Ser Thr Phe Pro Val Asp Arg Gly Trp Asp Cys Asn Thr Leu Phe Asp
3365 3370 3375

Pro Asp Pro Asp Arg Ala Gly Ser Thr Tyr Val Arg Glu Gly Ala Phe
3380 3385 3390

Leu Thr Gly Ala Asp Arg Phe Asp Ala Gly Phe Phe Gly Ile Ser Pro
3395 3400 3405

Arg Glu Ala Arg Ala Met Asp Pro Gln Gln Arg Leu Leu Leu Glu Val
3410 3415 3420

Ala Trp Glu Val Phe Glu Arg Ala Gly Ile Ala Pro Leu Ser Leu Arg

BNSDOCID: <WO___9946387A1_I_>

```
3425                3430                3435                3440

Gly Ser Arg Thr Gly Val Phe Ala Gly Thr Asn Gly Gln Asp His Gly
                3445                3450                3455

Ala Lys Val Ala Ala Ala Pro Glu Ala Ala Gly His Leu Leu Thr Gly
            3460                3465                3470

Asn Ala Ala Ser Val Leu Ala Gly Arg Leu Ser Tyr Thr Phe Gly Leu
        3475                3480                3485

Glu Gly Pro Ala Val Ala Val Asp Thr Ala Cys Ser Ser Ser Leu Val
    3490                3495                3500

Ala Leu His Leu Ala Cys Gln Ser Leu Arg Ser Gly Glu Cys Asp Met
3505                3510                3515                3520

Ala Leu Ala Gly Gly Val Thr Val Met Ser Thr Pro Leu Ala Phe Leu
                3525                3530                3535

Glu Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg Cys Lys Ser
            3540                3545                3550

Phe Ala Ala Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly Ala Gly Leu
        3555                3560                3565

Val Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly His Arg Val
    3570                3575                3580

Leu Ala Val Val Arg Gly Ser Ala Val Asn Gln Asp Gly Ala Ser Asn
3585                3590                3595                3600

Gly Leu Thr Ala Pro Asn Gly Pro Ser Gln Gln Arg Val Ile Arg Gln
                3605                3610                3615

Ala Leu Ala Asn Ala Gly Leu Ser Ala Ser Asp Val Asp Val Val Glu
            3620                3625                3630

Ala His Gly Thr Gly Thr Gly Leu Gly Asp Pro Ile Glu Ala Gln Ala
        3635                3640                3645

Leu Ile Ala Thr Tyr Gly Gln Glu Arg Asp Pro Glu Arg Ala Leu Trp
    3650                3655                3660

Leu Gly Ser Ile Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala Gly
3665                3670                3675                3680

Val Ala Gly Val Ile Lys Met Val Gln Ala Met Arg His Gly Glu Leu
                3685                3690                3695

Pro Ala Thr Leu His Val Asp Lys Pro Thr Pro Gln Val Asp Trp Ser
            3700                3705                3710

Ala Gly Ala Val Arg Leu Leu Thr Gly Asn Thr Pro Trp Pro Glu Ser
        3715                3720                3725

Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly Thr
    3730                3735                3740
```


BNSDOCID: <WO___9946387A1_I_>

Asn Ala His Leu Ile Leu Glu Gln Pro Pro Ser Glu Pro Ala Glu Ile
3745 3750 3755 3760

Asp Gln Ser Asp Arg Arg Val Thr Ala His Pro Ala Val Ile Pro Trp
3765 3770 3775

Met Leu Ser Ala Arg Ser Leu Ala Ala Leu Gln Ala Gln Ala Ala Ala
3780 3785 3790

Leu Gln Ala Arg Leu Asp Arg Gly Pro Gly Ala Ser Pro Leu Asp Leu
3795 3800 3805

Gly Tyr Ser Leu Ala Thr Thr Arg Ser Val Leu Asp Glu Arg Ala Val
3810 3815 3820

Val Trp Gly Ala Asp Arg Glu Ala Leu Leu Ser Arg Leu Ala Ala Leu
3825 3830 3835 3840

Ala Asp Gly Arg Thr Ala Pro Gly Val Ile Thr Gly Ser Ala Asn Ser
3845 3850 3855

Gly Gly Arg Ile Gly Phe Val Phe Ser Gly Gln Gly Ser Gln Trp Leu
3860 3865 3870

Gly Met Gly Lys Ala Leu Cys Ala Ala Phe Pro Ala Phe Ala Asp Ala
3875 3880 3885

Phe Glu Glu Ala Cys Asp Ala Leu Ser Ala His Leu Gly Ala Asp Val
3890 3895 3900

Arg Gly Val Leu Phe Gly Ala Asp Glu Gln Met Leu Asp Arg Thr Leu
3905 3910 3915 3920

Trp Ala Gln Ser Gly Ile Phe Ala Val Gln Val Gly Leu Leu Gly Leu
3925 3930 3935

Leu Arg Ser Trp Gly Val Arg Pro Ala Ala Val Leu Gly His Ser Val
3940 3945 3950

Gly Glu Leu Ala Ala Ala His Ala Ala Gly Val Leu Ser Leu Pro Asp
3955 3960 3965

Ala Ala Arg Leu Val Ala Ala Arg Ala His Leu Met Gln Ala Leu Pro
3970 3975 3980

Thr Gly Gly Ala Met Leu Ala Val Ala Thr Ser Glu Ala Ala Val Gly
3985 3990 3995 4000

Pro Leu Leu Ser Gly Val Cys Asp Arg Val Ser Ile Ala Ala Ile Asn
4005 4010 4015

Gly Pro Glu Ser Val Val Leu Ser Gly Asp Arg Asp Val Leu Val Glu
4020 4025 4030

Leu Ala Gly Glu Phe Asp Ala Arg Gly Leu Arg Thr Lys Trp Leu Arg
4035 4040 4045

BNSDOCID: <WO___9946387A1_I_>

```
Val Ser His Ala Phe His Ser His Arg Met Glu Pro Ile Leu Asp Glu
   4050                4055                4060

Tyr Ala Glu Thr Ala Arg Cys Val Glu Phe Gly Glu Pro Val Val Pro
4065                4070                4075                4080

Ile Val Ser Ala Ala Thr Gly Ala Leu Asp Thr Thr Gly Leu Met Cys
                4085                4090                4095

Ala Ala Asp Tyr Trp Thr Arg Gln Val Arg Asp Pro Val Arg Phe Gly
           4100                4105                4110

Asp Gly Val Arg Ala Leu Val Gly Gln Gly Val Asp Thr Ile Val Glu
       4115                4120                4125

Phe Gly Pro Asp Gly Ala Leu Ser Ala Leu Val Glu Gln Cys Leu Ala
   4130                4135                4140

Gly Ser Asp Gln Ala Gly Arg Val Ala Ala Ile Pro Leu Met Arg Arg
4145                4150                4155                4160

Asp Arg Asp Glu Val Glu Thr Ala Val Ala Ala Leu Ala His Val His
                4165                4170                4175

Val Arg Gly Gly Ala Val Asp Trp Ser Ala Cys Phe Ala Gly Thr Gly
           4180                4185                4190

Ala Arg Thr Val Glu Leu Pro Thr Tyr Ala Phe Gln Arg Gln Arg Tyr
       4195                4200                4205

Trp Leu Ala Gly Gln Ala Asp Gly Arg Gly Gly Asp Val Val Ala Asp
   4210                4215                4220

Pro Val Asp Ala Arg Phe Trp Glu Leu Val Glu Arg Ala Asp Pro Glu
4225                4230                4235                4240

Pro Leu Val Asp Glu Leu Cys Ile Asp Arg Asp Gln Pro Phe Arg Glu
                4245                4250                4255

Val Leu Pro Val Leu Ala Ser Trp Arg Glu Lys Gln Arg Gln Glu Ala
           4260                4265                4270

Leu Ala Asp Ser Trp Arg Tyr Gln Val Arg Trp Arg Ser Val Glu Val
       4275                4280                4285

Pro Ser Ala Ala Ala Leu Arg Gly Val Trp Leu Val Val Leu Pro Ala
   4290                4295                4300

Asp Val Pro Arg Asp Gln Pro Ala Val Val Ile Asp Ala Leu Ile Ala
4305                4310                4315                4320

Arg Gly Ala Glu Val Ala Val Leu Glu Leu Thr Glu Gln Asp Leu Gln
                4325                4330                4335

Arg Ser Ala Leu Val Asp Lys Val Arg Ala Val Ile Ala Asp Arg Thr
           4340                4345                4350

Glu Val Thr Gly Val Leu Ser Leu Leu Ala Met Asp Gly Met Pro Cys
```


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4355 4360 4365

Ala Ala His Pro His Leu Ser Arg Gly Val Ala Ala Thr Val Ile Leu
4370 4375 4380

Thr Gln Val Leu Gly Asp Ala Gly Val Ser Ala Pro Leu Trp Leu Ala
4385 4390 4395 4400

Thr Thr Gly Gly Val Glu Ala Gly Thr Glu Asp Gly Pro Ala Asp Pro
4405 4410 4415

Asp His Gly Leu Ile Trp Gly Leu Gly Arg Val Val Gly Leu Glu His
4420 4425 4430

Pro Gln Trp Trp Gly Gly Leu Ile Asp Leu Pro Glu Thr Leu Asp Glu
4435 4440 4445

Thr Ser Arg Asn Gly Leu Val Ala Ala Leu Ala Gly Thr Ala Ala Glu
4450 4455 4460

Asp Gln Leu Ala Val Arg Ser Ser Gly Leu Phe Val Arg Arg Val Val
4465 4470 4475 4480

Arg Ala Ala Arg Asn Pro Arg Ser Glu Thr Trp Arg Ser Arg Gly Thr
4485 4490 4495

Val Leu Ile Thr Gly Gly Thr Gly Ala Leu Gly Ala Glu Val Ala Arg
4500 4505 4510

Trp Leu Ala Arg Arg Gly Ala Glu His Leu Val Leu Ile Ser Arg Arg
4515 4520 4525

Gly Pro Glu Ala Pro Gly Ala Ala Asp Leu Gly Ala Glu Leu Thr Glu
4530 4535 4540

Leu Gly Val Lys Val Thr Val Leu Ala Cys Asp Val Thr Asp Arg Asp
4545 4550 4555 4560

Glu Leu Ala Ala Val Leu Ala Ala Val Pro Thr Glu Tyr Pro Leu Ser
4565 4570 4575

Ala Val Val His Thr Ala Gly Val Gly Thr Pro Ala Asn Leu Ala Glu
4580 4585 4590

Thr Thr Leu Ala Gln Phe Ala Asp Val Leu Ser Ala Lys Val Val Gly
4595 4600 4605

Ala Ala Asn Leu Asp Arg Leu Leu Gly Gly Gln Pro Leu Asp Ala Phe
4610 4615 4620

Val Leu Phe Ser Ser Ile Ser Gly Val Trp Gly Ala Gly Gly Gln Gly
4625 4630 4635 4640

Ala Tyr Ser Ala Ala Asn Ala Tyr Leu Asp Ala Leu Ala Glu Arg Arg
4645 4650 4655

Arg Ala Cys Gly Arg Pro Ala Thr Cys Ile Ala Trp Gly Pro Trp Ala
4660 4665 4670

BNSDOCID: <WO___9946387A1_I_>

```
Gly Ala Gly Met Ala Val Gln Glu Gly Asn Glu Ala His Leu Arg Arg
       4675                4680                4685

Arg Gly Leu Val Pro Met Glu Pro Gln Ser Ala Leu Phe Ala Leu Gln
   4690                4695                4700

Gln Ala Leu Ser Gln Arg Glu Thr Ala Ile Thr Val Ala Asp Val Asp
4705                4710                4715                4720

Trp Glu Arg Phe Ala Ala Ser Phe Thr Ala Ala Arg Pro Arg Pro Leu
               4725                4730                4735

Leu Glu Glu Ile Val Asp Leu Arg Pro Asp Thr Glu Thr Glu Glu Lys
           4740                4745                4750

His Gly Ala Gly Glu Leu Gly Gln Gln Leu Ala Ala Leu Pro Pro Ala
       4755                4760                4765

Glu Arg Gly His Leu Leu Leu Glu Val Val Leu Ala Glu Thr Ala Ser
   4770                4775                4780

Thr Leu Gly His Asp Ser Ala Glu Ala Val Gln Pro Asp Arg Thr Phe
4785                4790                4795                4800

Ala Glu Leu Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg
               4805                4810                4815

Leu Asn Ala Val Thr Gly Leu Arg Leu Pro Pro Thr Leu Val Phe Asp
           4820                4825                4830

His Pro Thr Pro Leu Ala Leu Ser Glu Gln Leu Val Pro Ala Leu Val
       4835                4840                4845

Ala Glu Pro Asp Asn Gly Ile Glu Ser Leu Leu Ala Glu Leu Asp Arg
   4850                4855                4860

Leu Asp Thr Thr Leu Ala Gln Gly Pro Ser Ile Pro Leu Glu Asp Gln
4865                4870                4875                4880

Ala Lys Val Ala Glu Arg Leu His Ala Leu Leu Ala Lys Trp Asp Gly
               4885                4890                4895

Ala Arg Asp Gly Thr Ala Arg Ala Thr Ser Pro Gln Ser Leu Thr Ala
           4900                4905                4910

Ala Thr Asp Asp Glu Ile Phe Asp Leu Ile Asp Arg Lys Phe Arg Arg
       4915                4920                4925
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<211> 5588
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<213> Saccharopolyspora spinosa

BNSDOCID: <WO___9946387A1_I_>

<400> 6

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Met Ala Asn Glu Glu Lys Leu Arg Glu Tyr Leu Lys Arg Val Val Val
 1               5                  10                  15

Glu Leu Glu Glu Ala His Glu Arg Leu His Glu Leu Glu Arg Gln Glu
            20                  25                  30

His Asp Pro Ile Ala Ile Val Ser Met Gly Cys Arg Tyr Pro Gly Gly
        35                  40                  45

Val Ser Thr Pro Glu Glu Leu Trp Arg Leu Val Val Asp Gly Gly Asp
    50                  55                  60

Ala Ile Ala Asn Phe Pro Glu Asp Arg Gly Trp Asn Leu Asp Glu Leu
65                  70                  75                  80

Phe Asp Pro Asp Pro Gly Arg Ala Gly Thr Ser Tyr Val Arg Glu Gly
                85                  90                  95

Gly Phe Leu Arg Gly Val Ala Asp Phe Asp Ala Gly Leu Phe Gly Ile
            100                 105                 110

Ser Pro Arg Glu Ala Gln Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
        115                 120                 125

Glu Ile Ser Trp Glu Val Phe Glu Arg Ala Gly Ile Asp Pro Phe Ser
    130                 135                 140

Leu Arg Gly Thr Lys Thr Gly Val Phe Ala Gly Leu Ile Tyr His Asp
145                 150                 155                 160

Tyr Ala Ser Arg Phe Arg Lys Thr Pro Ala Glu Phe Glu Gly Tyr Phe
                165                 170                 175

Ala Thr Gly Asn Ala Gly Ser Val Ala Ser Gly Arg Val Ala Tyr Thr
            180                 185                 190

Phe Gly Leu Glu Gly Pro Ala Val Thr Val Asp Thr Ala Cys Ser Ser
        195                 200                 205

Ser Leu Val Ala Leu His Leu Ala Cys Gln Ser Leu Arg Leu Gly Glu
    210                 215                 220

Cys Asp Leu Ala Leu Ala Gly Gly Ile Ser Val Met Ala Thr Pro Gly
225                 230                 235                 240

Ala Phe Val Glu Phe Ser Arg Gln Arg Ala Leu Ala Ser Asp Gly Arg
                245                 250                 255

Cys Lys Pro Phe Ala Asp Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
            260                 265                 270

Ala Gly Met Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
        275                 280                 285

His Pro Val Leu Ala Ala Val Val Gly Ser Ala Ile Asn Gln Asp Gly
    290                 295                 300
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BNSDOCID: <WO___9946387A1_I_>

```
Thr Ser Asn Gly Leu Thr Ala Pro Ser Gly Pro Ala Gln Gln Arg Val
305                 310                 315                 320

Ile Arg Gln Ala Leu Ala Asn Ala Gly Leu Ser Pro Ala Glu Val Asp
                325                 330                 335

Val Val Glu Ala His Gly Thr Gly Thr Ala Leu Gly Asp Pro Ile Glu
            340                 345                 350

Ala Gln Ala Leu Ile Ala Thr Tyr Gly Ala Asn Arg Ser Ala Asp His
        355                 360                 365

Pro Leu Leu Leu Gly Ser Leu Lys Ser Asn Ile Gly His Thr Gln Ala
    370                 375                 380

Ala Ala Gly Val Ala Gly Val Ile Lys Ser Val Leu Ala Ile Arg His
385                 390                 395                 400

Arg Glu Met Pro Arg Ser Leu His Ile Asp Gln Pro Ser Gln His Val
                405                 410                 415

Asp Trp Ser Ala Gly Ala Val Arg Leu Leu Thr Asp Ser Val Asp Trp
            420                 425                 430

Pro Asp Leu Gly Arg Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Met
        435                 440                 445

Ser Gly Thr Asn Ala His Leu Ile Val Glu Glu Val Ser Asp Glu Pro
    450                 455                 460

Val Ser Gly Ser Thr Glu Pro Thr Gly Ala Phe Pro Trp Pro Leu Ser
465                 470                 475                 480

Gly Lys Thr Glu Thr Ala Leu Arg Glu Gln Ala Ala Glu Leu Leu Ser
                485                 490                 495

Val Val Thr Glu His Pro Glu Pro Gly Leu Gly Asp Val Gly Tyr Ser
            500                 505                 510

Leu Ala Thr Gly Arg Ala Ala Met Glu His Arg Ala Val Val Val Ala
        515                 520                 525

Asp Asp Arg Asp Ser Phe Val Ala Gly Leu Thr Ala Leu Ala Ala Gly
    530                 535                 540

Val Pro Ala Ala Asn Val Val Gln Gly Ala Ala Asp Cys Lys Gly Lys
545                 550                 555                 560

Val Ala Phe Val Phe Pro Gly Gln Gly Ser His Trp Gln Gly Met Ala
                565                 570                 575

Arg Glu Leu Ser Glu Ser Ser Pro Val Phe Arg Arg Lys Leu Ala Glu
            580                 585                 590

Cys Ala Ala Ala Thr Ala Pro Tyr Val Asp Trp Ser Leu Leu Gly Val
        595                 600                 605

Leu Arg Gly Asp Pro Asp Ala Pro Ala Leu Asp Arg Asp Asp Val Ile
```


BNSDOCID: <WO___9946387A1_I_>

610 615 620

Gln Leu Ala Leu Phe Ala Met Met Val Ser Leu Ala Glu Leu Trp Arg
625 630 635 640

Ser Cys Gly Val Glu Pro Ala Ala Val Val Gly His Ser Gln Gly Glu
645 650 655

Ile Ala Ala Ala His Val Ala Gly Ala Leu Ser Leu Thr Asp Ala Val
660 665 670

Arg Ile Ile Ala Ala Arg Cys Asp Ala Val Ser Ala Leu Thr Gly Lys
675 680 685

Gly Gly Met Leu Ala Ile Ala Leu Pro Glu Ser Ala Val Val Lys Arg
690 695 700

Ile Ala Gly Leu Pro Glu Leu Thr Val Ala Ala Val Asn Gly Pro Gly
705 710 715 720

Ser Thr Val Val Ser Gly Glu Pro Ser Ala Leu Glu Arg Leu Gln Thr
725 730 735

Glu Leu Thr Ala Glu Asn Val Gln Thr Arg Arg Val Gly Ile Asp Tyr
740 745 750

Ala Ser His Ser Pro Gln Ile Ala Gln Val Gln Gly Arg Leu Leu Asp
755 760 765

Arg Leu Gly Glu Val Gly Ser Glu Pro Ala Glu Ile Ala Phe Tyr Ser
770 775 780

Thr Val Thr Gly Glu Arg Thr Asp Thr Gly Arg Leu Asp Ala Asp Tyr
785 790 795 800

Trp Tyr Gln Asn Leu Arg Gln Pro Val Arg Phe Gln Gln Thr Val Ala
805 810 815

Arg Met Ala Asp Gln Gly Tyr Arg Phe Phe Val Glu Val Ser Pro His
820 825 830

Pro Leu Leu Thr Ala Gly Ile Gln Glu Thr Leu Glu Ala Ala Asp Ala
835 840 845

Gly Gly Val Val Val Gly Ser Leu Arg Arg Gly Glu Gly Gly Ser Arg
850 855 860

Arg Trp Leu Thr Ser Leu Ala Glu Cys Gln Val Arg Gly Leu Pro Val
865 870 875 880

Asn Trp Glu Gln Val Phe Leu Asn Thr Gly Ala Arg Arg Val Pro Leu
885 890 895

Pro Thr Tyr Pro Phe Gln Arg Gln Arg Tyr Trp Leu Glu Ser Ala Glu
900 905 910

Tyr Asp Ala Gly Asp Leu Gly Ser Val Gly Leu Leu Ser Ala Glu His
915 920 925

BNSDOCID: <WO___9946387A1_I_>

```
Pro Leu Leu Gly Ala Ala Val Thr Leu Ala Asp Ala Gly Gly Phe Leu
    930                 935                 940

Leu Thr Gly Lys Leu Ser Val Lys Thr Gln Pro Trp Leu Ala Asp His
945                 950                 955                 960

Val Val Gly Gly Ala Ile Leu Leu Pro Gly Thr Ala Phe Val Glu Met
                965                 970                 975

Leu Ile Arg Ala Ala Asp Gln Val Gly Cys Asp Leu Ile Glu Glu Leu
            980                 985                 990

Ser Leu Thr Thr Pro Leu Val Leu Pro Ala Thr Gly Ala Val Gln Val
        995                1000                1005

Gln Ile Ala Val Gly Gly Pro Asp Glu Ala Gly Arg Arg Ser Val Arg
   1010                1015                1020

Val His Ser Cys Arg Asp Asp Ala Val Pro Gln Asp Ser Trp Thr Cys
1025                1030                1035                1040

His Ala Thr Gly Thr Leu Thr Ser Ser Asp His Gln Asp Ala Gly Gln
                1045                1050                1055

Gly Pro Asp Gly Ile Trp Pro Pro Asn Asp Ala Val Ala Val Pro Leu
            1060                1065                1070

Asp Ser Phe Tyr Ala Arg Ala Ala Glu Arg Gly Phe Asp Phe Gly Pro
        1075                1080                1085

Ala Phe Gln Gly Leu Gln Ala Ala Trp Lys Arg Gly Asp Glu Ile Phe
   1090                1095                1100

Ala Glu Val Gly Leu Pro Thr Ala His Arg Glu Asp Ala Gly Arg Phe
1105                1110                1115                1120

Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu Gln Ala Leu Gly Ala
                1125                1130                1135

Ala Glu Glu Asp Pro Asp Glu Gly Trp Leu Pro Phe Ala Trp Gln Gly
            1140                1145                1150

Val Ser Leu Lys Ala Thr Gly Ala Leu Ser Leu Arg Val His Leu Val
        1155                1160                1165

Pro Ala Gly Ala Asn Ala Val Ser Val Phe Thr Thr Asp Thr Thr Gly
   1170                1175                1180

Gln Ala Val Leu Ser Ile Asp Ser Leu Val Leu Arg Gln Ile Ser Asp
1185                1190                1195                1200

Lys Gln Leu Ala Ala Ala Arg Ala Met Glu His Glu Ser Leu Phe Arg
                1205                1210                1215

Val Asp Trp Lys Arg Ile Ser Pro Gly Ala Ala Lys Pro Val Ser Trp
            1220                1225                1230
```


BNSDOCID: <WO___9946387A1_I_>

Ala Val Ile Gly Asn Asp Glu Leu Ala Arg Ala Cys Gly Ser Ala Leu
1235 1240 1245

Gly Thr Glu Leu His Pro Asp Leu Thr Gly Leu Ala Asp Pro Pro Pro
1250 1255 1260

Asp Val Val Val Val Pro Cys Gly Ala Ser Arg Gln Asp Leu Asp Val
1265 1270 1275 1280

Ala Ser Glu Ala Arg Ala Ala Thr Gln Arg Met Leu Asp Leu Ile Gln
1285 1290 1295

Asp Trp Leu Ala Ala Ala Arg Phe Ala Gly Ser Arg Leu Val Val Val
1300 1305 1310

Thr Cys Gly Ala Ala Ser Thr Gly Pro Ala Glu Gly Val Ser Asp Leu
1315 1320 1325

Val His Ala Ala Ser Trp Gly Leu Leu Arg Ser Ala Gln Ser Glu Asn
1330 1335 1340

Pro Asp Arg Phe Val Leu Val Asp Val Asp Gly Thr Ala Glu Ser Trp
1345 1350 1355 1360

Arg Ala Leu Ala Ala Ala Val Arg Ser Gly Glu Pro Gln Leu Ala Leu
1365 1370 1375

Arg Ala Gly Glu Val Arg Val Pro Arg Leu Ala Arg Cys Val Ala Ala
1380 1385 1390

Glu Asp Ser Arg Ile Pro Val Pro Gly Ala Asp Gly Thr Val Leu Ile
1395 1400 1405

Ser Gly Gly Thr Gly Leu Leu Gly Gly Leu Val Ala Arg His Leu Val
1410 1415 1420

Ala Glu Arg Gly Val Arg Arg Leu Val Leu Ala Gly Arg Arg Gly Trp
1425 1430 1435 1440

Ser Ala Pro Gly Val Thr Asp Leu Val Asp Glu Leu Val Gly Leu Gly
1445 1450 1455

Ala Ala Val Glu Val Ala Ser Cys Asp Val Gly Asp Arg Ala Gln Leu
1460 1465 1470

Asp Arg Leu Leu Thr Thr Ile Ser Ala Glu Phe Pro Leu Arg Gly Val
1475 1480 1485

Val His Ala Ala Gly Ala Leu Ala Asp Gly Val Val Glu Ser Leu Thr
1490 1495 1500

Pro Glu His Val Ala Lys Val Phe Gly Pro Lys Ala Ala Gly Ala Trp
1505 1510 1515 1520

His Leu His Glu Leu Thr Leu Asp Leu Asp Leu Ser Phe Phe Val Leu
1525 1530 1535

Phe Ser Ser Phe Ser Gly Val Ala Gly Ala Ala Gly Gln Gly Asn Tyr

BNSDOCID: <WO___9946387A1_I_>

```
          1540                1545                1550

Ala Ala Ala Asn Ala Phe Leu Asp Gly Leu Ala Gln His Arg Arg Thr
       1555                1560                1565

Ala Gly Leu Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro
   1570                1575                1580

Ser Gly Met Thr Gly Ala Leu Asp Ala Ala Gly Arg Ser Arg Ile Ala
1585                1590                1595                1600

Arg Thr Asn Pro Pro Met Ser Ala Pro Asp Gly Leu Arg Leu Phe Glu
               1605                1610                1615

Met Ala Phe Arg Val Pro Gly Glu Ser Leu Leu Val Pro Val His Val
           1620                1625                1630

Asp Leu Asn Ala Leu Arg Ala Asp Ala Ala Asp Gly Gly Val Pro Ala
       1635                1640                1645

Leu Leu Arg Asp Leu Val Pro Ala Pro Val Arg Arg Ser Ala Val Asn
   1650                1655                1660

Glu Ser Ala Asp Val Asn Gly Leu Val Gly Arg Leu Arg Arg Leu Pro
1665                1670                1675                1680

Asp Leu Asp Gln Glu Thr Gln Leu Leu Gly Leu Val Arg Glu His Val
               1685                1690                1695

Ser Ala Val Leu Gly His Ser Gly Ala Val Glu Val Gly Ala Asp Arg
           1700                1705                1710

Ala Phe Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Phe Arg
       1715                1720                1725

Asn Arg Leu Gly Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val
   1730                1735                1740

Phe Asp Tyr Pro Thr Pro Arg Ala Leu Val Arg Phe Leu Leu Asp Lys
1745                1750                1755                1760

Leu Ile Gly Gly Val Glu Ala Pro Thr Pro Ala Pro Ala Ala Val Ala
               1765                1770                1775

Ala Val Thr Ala Asp Asp Pro Val Val Ile Val Gly Met Gly Cys Arg
           1780                1785                1790

Tyr Pro Gly Gly Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala
       1795                1800                1805

Gly Gly Leu Asp Ala Val Ala Glu Phe Pro Asp Asp Arg Gly Trp Asp
   1810                1815                1820

Gln Ala Gly Leu Phe Asp Pro Asp Pro Asp Arg Leu Gly Thr Ser Tyr
1825                1830                1835                1840

Val Cys Glu Gly Gly Phe Leu Arg Asp Ala Ala Glu Phe Asp Ala Gly
               1845                1850                1855
```


BNSDOCID: <WO___9946387A1_I_>

Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln
1860 1865 1870

Arg Leu Leu Leu Glu Val Ala Trp Glu Thr Val Glu Arg Ala Gly Ile
1875 1880 1885

Asp Pro Leu Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu
1890 1895 1900

Met His His Asp Tyr Gly Ala Arg Phe Ile Thr Arg Ala Pro Glu Gly
1905 1910 1915 1920

Phe Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Gly Val Phe Ser Gly
1925 1930 1935

Arg Val Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp
1940 1945 1950

Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala
1955 1960 1965

Leu Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val
1970 1975 1980

Met Ala Thr Pro Gly Met Phe Val Glu Phe Ser Arg Gln Arg Gly Leu
1985 1990 1995 2000

Ala Ala Asp Gly Arg Cys Lys Ser Phe Ala Ala Ala Ala Asp Gly Thr
2005 2010 2015

Gly Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp
2020 2025 2030

Ala Arg Arg Asn Gly His Ala Val Leu Ala Val Val Arg Gly Ser Ala
2035 2040 2045

Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro
2050 2055 2060

Ser Gln Gln Arg Val Ile Thr Gln Ala Leu Ala Ser Ala Gly Leu Ser
2065 2070 2075 2080

Val Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu
2085 2090 2095

Gly Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Gln Gly
2100 2105 2110

Arg Asp Ser Asp Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile
2115 2120 2125

Gly His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val
2130 2135 2140

Met Ala Met Arg His Gly Gln Leu Pro Ala Thr Leu His Val Asp Glu
2145 2150 2155 2160

BNSDOCID: <WO___9946387A1_I_>

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Pro Thr Ser Glu Val Asp Trp Ser Ala Gly Asp Val Gln Leu Leu Thr
                2165                2170                2175

Glu Asn Thr Pro Trp Pro Gly Asn Ser His Pro Arg Arg Val Gly Val
            2180                2185                2190

Ser Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln
        2195                2200                2205

Ala Ser Lys Thr Pro Asp Glu Thr Ala Asp Lys Ser Gly Pro Asp Ser
    2210                2215                2220

Glu Ser Thr Val Asp Leu Pro Ala Val Pro Leu Ile Val Ser Gly Arg
2225                2230                2235                2240

Thr Pro Ala Ala Leu Ser Ala Gln Ala Ser Ala Leu Leu Ser Tyr Leu
                2245                2250                2255

Gly Glu Arg Gly Asp Ile Ser Thr Leu Asp Ala Ala Phe Ser Leu Ala
            2260                2265                2270

Ser Ser Arg Ala Ala Leu Glu Glu Arg Ala Val Val Leu Gly Ala Asp
        2275                2280                2285

Arg Glu Thr Leu Leu Ser Gly Leu Glu Ala Leu Ala Ser Gly Arg Glu
    2290                2295                2300

Ala Ser Gly Val Val Ser Gly Ser Pro Val Ser Gly Gly Val Gly Phe
2305                2310                2315                2320

Val Phe Ala Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Gly Leu
                2325                2330                2335

Tyr Ser Val Phe Pro Val Phe Ala Asp Ala Phe Asp Glu Ala Cys Ala
            2340                2345                2350

Gly Leu Asp Ala His Leu Gly Gln Asp Val Gly Val Arg Asp Val Val
        2355                2360                2365

Phe Gly Ser Asp Gly Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser
    2370                2375                2380

Gly Leu Phe Ala Leu Gln Val Gly Leu Leu Ser Leu Leu Gly Ser Trp
2385                2390                2395                2400

Gly Val Arg Pro Gly Val Val Leu Gly His Ser Val Gly Glu Phe Ala
                2405                2410                2415

Ala Ala Val Ala Ala Gly Val Leu Ser Leu Pro Asp Ala Ala Arg Met
            2420                2425                2430

Val Ala Gly Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala
        2435                2440                2445

Met Leu Ala Val Ala Ala Gly Glu Glu Gln Leu Arg Pro Leu Leu Ala
    2450                2455                2460

Asp Arg Val Asp Gly Ala Gly Ile Ala Ala Val Asn Ala Pro Glu Ser
```


BNSDOCID: <WO___9946387A1_I_>

2465 2470 2475 2480

Val Val Leu Ser Gly Asp Arg Glu Val Leu Asp Asp Ile Ala Gly Ala
2485 2490 2495

Leu Asp Gly Gln Gly Ile Arg Trp Arg Arg Leu Arg Val Ser His Ala
2500 2505 2510

Phe His Ser Tyr Arg Met Asp Pro Met Leu Gln Glu Phe Ala Glu Ile
2515 2520 2525

Ala Arg Ser Val Asp Tyr Arg Arg Gly Asp Leu Pro Val Val Ser Thr
2530 2535 2540

Leu Thr Gly Glu Leu Asp Thr Ala Gly Val Met Ala Thr Pro Glu Tyr
2545 2550 2555 2560

Trp Val Arg Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Arg
2565 2570 2575

Val Leu Ala Gln Gln Gly Val Ala Thr Ile Phe Glu Leu Gly Pro Asp
2580 2585 2590

Ala Thr Leu Ser Ala Leu Ile Pro Asp Cys His Ser Trp Ala Asp Gln
2595 2600 2605

Ala Met Pro Ile Pro Met Leu Arg Lys Asp Arg Thr Glu Thr Glu Thr
2610 2615 2620

Val Val Ala Ala Val Ala Arg Ala His Thr Arg Gly Val Pro Val Glu
2625 2630 2635 2640

Trp Ser Ala Tyr Phe Ala Gly Thr Gly Ala Arg Arg Val Glu Leu Pro
2645 2650 2655

Thr Tyr Ala Phe Gln Arg Gln Arg Tyr Trp Leu Glu Thr Ser Asp Tyr
2660 2665 2670

Gly Asp Val Thr Gly Ile Gly Leu Ala Ala Ala Glu His Pro Leu Leu
2675 2680 2685

Gly Ala Val Val Ala Leu Ala Asp Gly Asp Gly Met Val Leu Thr Gly
2690 2695 2700

Arg Leu Ser Val Gly Thr His Pro Trp Leu Ala Gln His Arg Val Leu
2705 2710 2715 2720

Gly Glu Val Val Val Pro Gly Thr Ala Ile Leu Glu Met Ala Leu His
2725 2730 2735

Ala Gly Ala Arg Leu Gly Cys Asp Arg Val Glu Glu Leu Thr Leu Glu
2740 2745 2750

Thr Pro Leu Val Val Pro Glu Arg Ala Ala Gly Ala Gly Ser Arg Gly
2755 2760 2765

Pro Ala Gly Gly Thr Thr Val Ser Ile Glu Thr Ala Glu Glu Arg Val
2770 2775 2780

BNSDOCID: <WO___9946387A1_I_>

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Arg Thr Asn Asp Ala Ile Glu Ile Gln Leu Leu Val Asn Ala Pro Asp
2785                2790                2795                2800

Glu Gly Gly Arg Arg Arg Val Ser Leu Tyr Ser Arg Pro Ala Gly Gly
                2805                2810                2815

Ser Arg Gly Gly Gly Trp Thr Arg His Ala Thr Gly Glu Leu Val Val
            2820                2825                2830

Gly Thr Thr Gly Gly Arg Ala Val Pro Asp Trp Ser Ala Glu Gly Ala
        2835                2840                2845

Glu Ser Ile Ala Leu Asp Glu Phe Tyr Val Ala Leu Ala Gly Asn Gly
    2850                2855                2860

Phe Glu Tyr Gly Pro Leu Phe Gln Gly Leu Gln Ala Ala Trp Arg Arg
2865                2870                2875                2880

Gly Asp Glu Val Leu Ala Glu Ile Ala Pro Pro Ala Glu Ala Asp Ala
                2885                2890                2895

Met Ala Ser Gly Tyr Leu Leu Asp Pro Ala Leu Leu Asp Ala Ala Leu
            2900                2905                2910

Gln Ala Ser Ala Leu Gly Asp Arg Pro Glu Gln Gly Gly Ala Trp Leu
        2915                2920                2925

Pro Phe Ser Phe Thr Gly Val Glu Leu Ser Ala Pro Ala Gly Thr Ile
    2930                2935                2940

Ser Arg Val Arg Leu Glu Thr Arg Arg Pro Asp Ala Ile Ser Val Ala
2945                2950                2955                2960

Val Met Asp Glu Ser Gly Arg Leu Leu Ala Ser Ile Asp Ser Leu Arg
                2965                2970                2975

Leu Arg Ser Val Ser Ser Gly Gln Leu Ala Asn Arg Asp Ala Val Arg
            2980                2985                2990

Asp Ala Leu Phe Glu Val Thr Trp Glu Pro Val Ala Thr Gln Ser Thr
        2995                3000                3005

Glu Pro Gly Arg Trp Ala Leu Leu Gly Asp Thr Ala Cys Gly Lys Asp
    3010                3015                3020

Asp Leu Ile Lys Leu Ala Thr Asp Ser Ala Asp Arg Cys Ala Asp Leu
3025                3030                3035                3040

Ala Ala Leu Ala Glu Lys Leu Asp Ser Ser Ala Leu Val Pro Asp Val
                3045                3050                3055

Val Val Tyr Cys Ala Gly Glu Gln Ala Asp Pro Gly Thr Gly Ala Ala
            3060                3065                3070

Ala Leu Ala Glu Thr Gln Gln Thr Leu Ala Leu Leu Gln Ala Trp Leu
        3075                3080                3085
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BNSDOCID: <WO___9946387A1_I_>

Ala Glu Pro Arg Leu Ala Glu Ala Arg Leu Val Val Val Thr Cys Ala
3090 3095 3100

Ala Val Thr Thr Ala Pro Ser Asp Gly Ala Ser Glu Leu Ala His Ala
3105 3110 3115 3120

Pro Leu Trp Gly Leu Leu Arg Ala Ala Gln Val Glu Asn Pro Gly Gln
3125 3130 3135

Phe Val Leu Ala Asp Val Asp Gly Thr Ala Glu Ser Trp Arg Ala Leu
3140 3145 3150

Pro Ser Ala Leu Gly Ser Met Glu Pro Gln Leu Ala Leu Arg Lys Gly
3155 3160 3165

Ala Val Arg Ala Pro Arg Leu Ala Ser Val Ala Gly Gln Ile Asp Val
3170 3175 3180

Pro Ala Val Val Ala Asp Pro Asp Arg Thr Val Leu Ile Ser Gly Gly
3185 3190 3195 3200

Thr Gly Leu Leu Gly Gly Ala Val Ala Arg His Leu Val Thr Glu Arg
3205 3210 3215

Gly Val Arg Arg Leu Val Leu Thr Gly Arg Arg Gly Trp Asp Ala Pro
3220 3225 3230

Gly Ile Thr Glu Leu Val Gly Glu Leu Asn Gly Leu Gly Ala Val Val
3235 3240 3245

Asp Val Val Ala Cys Asp Val Ala Asp Arg Ala Asp Leu Glu Ser Leu
3250 3255 3260

Leu Ala Ala Val Pro Ala Glu Phe Pro Leu Cys Gly Val Val His Ala
3265 3270 3275 3280

Ala Gly Ala Leu Ala Asp Gly Val Ile Glu Ser Leu Ser Pro Asp Asp
3285 3290 3295

Val Gly Ala Val Phe Gly Pro Lys Ala Ala Gly Ala Trp Asn Leu His
3300 3305 3310

Glu Leu Thr Arg Asp Thr Asp Leu Ser Phe Phe Ala Leu Phe Ser Ser
3315 3320 3325

Leu Ser Gly Val Ala Gly Ala Pro Gly Gln Gly Asn Tyr Ala Ala Ala
3330 3335 3340

Asn Ala Phe Leu Asp Ala Leu Ala His Tyr Arg Arg Ser Gln Gly Leu
3345 3350 3355 3360

Pro Ala Val Ser Leu Ala Trp Gly Leu Trp Glu Gln Pro Ser Gly Met
3365 3370 3375

Thr Glu Thr Leu Ser Glu Val Asp Arg Ser Arg Ile Ala Arg Ala Asn
3380 3385 3390

Pro Pro Leu Ser Thr Lys Glu Gly Leu Arg Leu Phe Asp Ala Gly Leu

BNSDOCID: <WO___9946387A1_I_>

3395 3400 3405

Ala Leu Asp Arg Ala Ala Val Val Pro Ala Lys Leu Asp Arg Thr Phe
3410 3415 3420

Leu Ala Glu Gln Ala Arg Ser Gly Ser Leu Pro Ala Leu Leu Thr Ala
3425 3430 3435 3440

Leu Val Pro Pro Ile Arg Arg Asn Arg Arg Ala Ser Gly Thr Glu Leu
3445 3450 3455

Ala Asp Glu Gly Thr Leu Leu Gly Val Val Arg Glu His Ala Ala Ala
3460 3465 3470

Val Leu Gly Tyr Ser Ser Ala Ala Asp Val Gly Val Glu Arg Ala Phe
3475 3480 3485

Arg Asp Leu Gly Phe Asp Ser Leu Ser Gly Val Glu Leu Arg Asn Arg
3490 3495 3500

Leu Ala Gly Val Leu Gly Val Arg Leu Pro Ala Thr Ala Val Phe Asp
3505 3510 3515 3520

Tyr Pro Thr Pro Arg Ala Leu Ala Arg Phe Leu His Gln Glu Leu Ala
3525 3530 3535

Asp Glu Ile Ala Thr Thr Pro Ala Pro Val Thr Thr Thr Arg Ala Pro
3540 3545 3550

Val Ala Glu Asp Asp Leu Val Ala Ile Val Gly Met Gly Cys Arg Phe
3555 3560 3565

Pro Gly Gln Val Ser Ser Pro Glu Glu Leu Trp Arg Leu Val Ala Gly
3570 3575 3580

Gly Val Asp Ala Val Ala Asp Phe Pro Ala Asp Arg Gly Trp Asp Leu
3585 3590 3595 3600

Ala Gly Leu Phe Asp Pro Asp Pro Glu Arg Ala Gly Lys Thr Tyr Val
3605 3610 3615

Arg Glu Gly Ala Phe Leu Thr Asp Ala Asp Arg Phe Asp Ala Gly Phe
3620 3625 3630

Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg
3635 3640 3645

Leu Leu Leu Glu Leu Ser Trp Glu Ala Ile Glu Arg Ala Gly Ile Asp
3650 3655 3660

Pro Gly Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Leu Met
3665 3670 3675 3680

Tyr His Asp Tyr Gly Ala Arg Phe Ala Ser Arg Ala Pro Glu Gly Phe
3685 3690 3695

Glu Gly Tyr Leu Gly Asn Gly Ser Ala Gly Ser Val Ala Ser Gly Arg
3700 3705 3710

BNSDOCID: <WO___9946387A1_I_>

Ile Ala Tyr Ser Phe Gly Phe Glu Gly Pro Ala Val Thr Val Asp Thr
3715 3720 3725

Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Gly Gln Ser Leu
3730 3735 3740

Arg Ser Gly Glu Cys Asp Leu Ala Leu Ala Gly Gly Val Thr Val Met
3745 3750 3755 3760

Ser Thr Pro Gly Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Leu Ala
3765 3770 3775

Pro Asp Gly Arg Cys Lys Ser Phe Ala Glu Ser Ala Asp Gly Thr Gly
3780 3785 3790

Trp Gly Glu Gly Ala Gly Leu Val Leu Leu Glu Arg Leu Ser Asp Ala
3795 3800 3805

Arg Arg Asn Gly His Arg Val Leu Ala Val Val Arg Gly Ser Ala Val
3810 3815 3820

Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ser
3825 3830 3835 3840

Gln Gln Arg Val Ile Gln Gln Ala Leu Ala Ser Ala Gly Leu Ser Val
3845 3850 3855

Ser Asp Val Asp Ala Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly
3860 3865 3870

Asp Pro Ile Glu Ala Gln Ala Leu Ile Ala Thr Tyr Gly Arg Asp Arg
3875 3880 3885

Asp Pro Gly Arg Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly
3890 3895 3900

His Thr Gln Ala Ala Ala Gly Val Ala Gly Val Ile Lys Met Val Met
3905 3910 3915 3920

Ala Met Arg His Gly Gln Leu Pro Arg Thr Leu His Val Asp Ala Pro
3925 3930 3935

Ser Ser Gln Val Asp Trp Ser Ala Gly Arg Val Gln Leu Leu Thr Glu
3940 3945 3950

Asn Thr Pro Trp Pro Asp Ser Gly Arg Pro Cys Arg Val Gly Val Ser
3955 3960 3965

Ser Phe Gly Ile Ser Gly Thr Asn Ala His Val Ile Leu Glu Gln Ser
3970 3975 3980

Thr Gly Gln Met Asp Gln Ala Ala Glu Pro Asp Ser Ser Pro Val Leu
3985 3990 3995 4000

Asp Val Pro Val Val Pro Trp Val Val Ser Gly Lys Thr Pro Glu Ala
4005 4010 4015

BNSDOCID: <WO___9946387A1_I_>

Leu Ser Ala Gln Ala Ala Thr Leu Ala Thr Tyr Leu Asp Gln Asn Val
4020 4025 4030

Asp Val Ser Pro Leu Asp Val Gly Ile Ser Leu Ala Val Thr Arg Ser
4035 4040 4045

Ala Leu Asp Glu Arg Ala Val Val Leu Gly Ser Asp Arg Asp Thr Leu
4050 4055 4060

Leu Ser Gly Leu Asn Ala Leu Ala Ala Gly His Glu Ala Ala Gly Val
4065 4070 4075 4080

Val Thr Gly Pro Val Gly Ile Gly Gly Arg Thr Gly Phe Val Phe Ala
4085 4090 4095

Gly Gln Gly Gly Gln Trp Leu Gly Met Gly Arg Arg Leu Tyr Ser Glu
4100 4105 4110

Phe Pro Ala Phe Ala Gly Ala Phe Asp Glu Ala Cys Ala Glu Leu Asp
4115 4120 4125

Ala Asn Leu Gly Arg Glu Val Gly Val Arg Asp Val Val Phe Gly Ser
4130 4135 4140

Asp Glu Ser Leu Leu Asp Arg Thr Leu Trp Ala Gln Ser Gly Leu Phe
4145 4150 4155 4160

Ala Leu Gln Val Gly Leu Trp Glu Leu Leu Gly Thr Trp Gly Val Arg
4165 4170 4175

Pro Ser Val Val Leu Gly His Ser Val Gly Glu Leu Ala Ala Ala Phe
4180 4185 4190

Ala Ala Gly Val Leu Ser Met Ala Glu Ala Ala Arg Leu Val Ala Gly
4195 4200 4205

Arg Ala Arg Leu Met Gln Ala Leu Pro Ser Gly Gly Ala Met Leu Ala
4210 4215 4220

Val Ser Ala Thr Glu Ala Arg Val Gly Pro Leu Leu Asp Gly Val Arg
4225 4230 4235 4240

Asp Arg Val Gly Val Ala Ala Val Asn Ala Pro Gly Ser Val Val Leu
4245 4250 4255

Ser Gly Asp Arg Asp Val Leu Asp Gly Ile Ala Gly Arg Leu Asp Gly
4260 4265 4270

Gln Gly Ile Arg Ser Arg Trp Leu Arg Val Ser His Ala Phe His Ser
4275 4280 4285

His Arg Met Asp Pro Met Leu Ala Glu Phe Ala Glu Leu Ala Arg Ser
4290 4295 4300

Val Asp Tyr Arg Ser Pro Arg Leu Pro Ile Val Ser Thr Leu Thr Gly
4305 4310 4315 4320

Asn Leu Asp Asp Val Gly Val Met Ala Thr Pro Glu Tyr Trp Val Arg

BNSDOCID: <WO___9946387A1_I_>

4325 4330 4335

Gln Val Arg Glu Pro Val Arg Phe Ala Asp Gly Val Gln Ala Leu Val
4340 4345 4350

Asp Gln Gly Val Asp Thr Ile Val Glu Leu Gly Pro Asp Gly Ala Leu
4355 4360 4365

Ser Ser Leu Val Gln Glu Cys Val Ala Glu Ser Gly Arg Ala Thr Gly
4370 4375 4380

Ile Pro Leu Val Arg Arg Asp Arg Asp Glu Val Arg Thr Val Leu Asp
4385 4390 4395 4400

Ala Leu Ala Gln Thr His Thr Arg Gly Gly Ala Val Asp Trp Gly Ser
4405 4410 4415

Phe Phe Ala Gly Thr Arg Ala Thr Gln Val Asp Leu Pro Thr Tyr Ala
4420 4425 4430

Phe Gln Arg Gln Arg Tyr Trp Leu Glu Pro Ser Asp Ser Gly Asp Val
4435 4440 4445

Thr Gly Val Gly Leu Thr Gly Ala Glu His Pro Leu Leu Gly Ala Val
4450 4455 4460

Val Pro Val Ala Gly Gly Asp Glu Val Leu Leu Thr Gly Arg Leu Ser
4465 4470 4475 4480

Val Gly Thr His Pro Trp Leu Ala Glu His Arg Val Leu Gly Glu Val
4485 4490 4495

Val Val Pro Gly Thr Ala Leu Leu Glu Met Ala Trp Arg Ala Gly Ser
4500 4505 4510

Gln Val Gly Cys Glu Arg Val Glu Glu Leu Thr Leu Glu Ala Pro Leu
4515 4520 4525

Val Leu Pro Glu Arg Gly Ala Ala Ala Val Gln Leu Ala Val Gly Ala
4530 4535 4540

Pro Asp Glu Ala Gly Arg Arg Ser Leu Gln Leu Tyr Ser Arg Gly Ala
4545 4550 4555 4560

Asp Glu Asp Gly Asp Trp Arg Arg Ile Ala Ser Gly Leu Leu Ala Gln
4565 4570 4575

Ala Asn Ala Val Pro Pro Ala Asp Ser Thr Ala Trp Pro Pro Asp Gly
4580 4585 4590

Ala Gly Gln Val Asp Leu Ala Glu Phe Tyr Glu Arg Leu Ala Glu Arg
4595 4600 4605

Gly Leu Thr Tyr Gly Pro Val Phe Gln Gly Leu Arg Ala Ala Trp Arg
4610 4615 4620

His Gly Asp Asp Ile Phe Ala Glu Leu Ala Gly Ser Pro Asp Ala Ser
4625 4630 4635 4640

BNSDOCID: <WO___9946387A1_I_>

```
Gly Phe Gly Ile His Pro Ala Leu Leu Asp Ala Ala Leu His Ala Met
                4645                4650                4655

Ala Leu Gly Ala Ser Pro Asp Ser Glu Ala Arg Leu Pro Phe Ser Trp
            4660                4665                4670

Arg Gly Ala Gln Leu Tyr Arg Ala Glu Gly Ala Ala Leu Arg Val Arg
        4675                4680                4685

Leu Ser Pro Leu Gly Ser Gly Ala Val Ser Leu Thr Leu Val Asp Ala
    4690                4695                4700

Thr Gly Arg Arg Val Ala Ala Val Glu Ser Leu Ser Thr Arg Pro Val
4705                4710                4715                4720

Ser Thr Asp Gln Ile Gly Ala Gly Arg Gly Asp Gln Glu Arg Leu Leu
                4725                4730                4735

His Val Glu Trp Val Arg Ser Ala Glu Ser Ala Gly Met Ser Leu Thr
            4740                4745                4750

Ser Cys Ala Val Val Gly Leu Gly Glu Pro Glu Trp His Ala Ala Leu
        4755                4760                4765

Lys Thr Thr Gly Val Gln Val Glu Ser His Ala Asp Leu Ala Ser Leu
    4770                4775                4780

Ala Thr Glu Val Ala Lys Arg Gly Ser Ala Pro Gly Ala Val Ile Val
4785                4790                4795                4800

Pro Cys Pro Arg Pro Arg Ala Met Gln Glu Leu Pro Thr Ala Ala Arg
                4805                4810                4815

Arg Ala Thr Gln Gln Ala Met Ala Met Leu Gln Gln Trp Leu Ala Asp
            4820                4825                4830

Asp Arg Phe Val Ser Thr Arg Leu Ile Leu Leu Thr His Arg Ala Val
        4835                4840                4845

Ser Ala Val Ala Gly Glu Asp Val Leu Asp Leu Val His Ala Pro Leu
    4850                4855                4860

Trp Gly Leu Val Arg Ser Ala Gln Ala Glu His Pro Asp Arg Phe Ala
4865                4870                4875                4880

Leu Ile Asp Met Asp Asp Glu Arg Ala Ser Gln Thr Ala Leu Ala Glu
                4885                4890                4895

Ala Leu Thr Ala Gly Glu Ala Gln Leu Ala Val Arg Ser Gly Val Val
            4900                4905                4910

Leu Ala Pro Arg Leu Gly Gln Val Lys Val Ser Gly Gly Glu Ala Phe
        4915                4920                4925

Arg Trp Asp Glu Gly Thr Val Leu Val Thr Gly Gly Thr Gly Gly Leu
    4930                4935                4940
```


BNSDOCID: <WO___9946387A1_I_>

Gly Ala Leu Leu Ala Arg His Leu Val Ser Ala His Gly Val Arg His
4945 4950 4955 4960

Leu Leu Leu Ala Ser Arg Arg Gly Leu Ala Ala Pro Gly Ala Asp Glu
4965 4970 4975

Leu Val Ala Glu Leu Glu Gln Ala Gly Ala Asp Val Ala Val Val Ala
4980 4985 4990

Cys Asp Ser Ala Asp Arg Asp Ser Leu Ala Arg Leu Val Ala Ser Val
4995 5000 5005

Pro Ala Glu Asn Pro Leu Arg Val Val Val His Ala Ala Gly Val Leu
5010 5015 5020

Asp Asp Gly Val Leu Met Ser Met Ser Pro Glu Arg Leu Asp Ala Val
5025 5030 5035 5040

Leu Arg Pro Lys Val Asp Ala Ala Trp Tyr Leu His Glu Leu Thr Arg
5045 5050 5055

Glu Leu Gly Leu Ser Ala Phe Val Leu Phe Ser Ser Val Ala Gly Leu
5060 5065 5070

Phe Gly Gly Ala Gly Gln Ser Asn Tyr Ala Ala Gly Asn Ala Phe Leu
5075 5080 5085

Asp Ala Leu Ala His Cys Arg Gln Ala Gln Gly Leu Pro Ala Leu Ser
5090 5095 5100

Leu Ala Ser Gly Leu Trp Ala Ser Ile Asp Gly Met Ala Gly Asp Leu
5105 5110 5115 5120

Ala Ala Ala Asp Val Glu Arg Leu Ser Arg Ala Gly Ile Gly Pro Leu
5125 5130 5135

Ser Ala Pro Gly Gly Leu Ala Leu Phe Asp Ala Ala Val Gly Ser Asp
5140 5145 5150

Glu Pro Leu Leu Ala Pro Val Arg Leu Asp Val Glu Ala Leu Arg Val
5155 5160 5165

Gln Ala Arg Ser Val Gln Thr Arg Ile Pro Glu Met Leu His Gly Met
5170 5175 5180

Ala Met Gly Pro Ser Arg Arg Thr Pro Phe Thr Ser Arg Val Glu Pro
5185 5190 5195 5200

Leu His Glu Arg Leu Ala Gly Leu Ser Glu Gly Glu Arg Arg Gln Gln
5205 5210 5215

Val Leu Gln Arg Val Arg Ala Asp Ile Ala Val Val Leu Gly His Gly
5220 5225 5230

Arg Ser Ser Asp Val Asp Ile Glu Lys Pro Leu Ala Glu Leu Gly Phe
5235 5240 5245

Asp Ser Leu Thr Ala Ile Glu Leu Arg Asn Arg Leu Ala Thr Ala Thr

BNSDOCID: <WO___9946387A1_I_>

5250 5255 5260

Gly Leu Arg Leu Pro Ala Thr Leu Ala Phe Asp His Gly Thr Ala Ala
5265 5270 5275 5280

Ala Leu Ala Gln His Val Cys Ala Gln Leu Gly Thr Ala Thr Ala Pro
5285 5290 5295

Ala Pro Arg Arg Thr Asp Asp Asn Asp Ala Thr Glu Pro Val Arg Ser
5300 5305 5310

Leu Phe Gln Gln Ala Tyr Ala Ala Gly Arg Ile Leu Asp Gly Met Asp
5315 5320 5325

Leu Val Lys Val Ala Ala Gln Leu Arg Pro Val Phe Gly Ser Pro Gly
5330 5335 5340

Glu Leu Glu Ser Leu Pro Lys Pro Val Gln Leu Ser Arg Gly Pro Glu
5345 5350 5355 5360

Glu Leu Ala Leu Val Cys Met Pro Ala Leu Ile Gly Met Pro Pro Ala
5365 5370 5375

Gln Gln Tyr Ala Arg Ile Ala Ala Gly Phe Arg Asp Val Arg Asp Val
5380 5385 5390

Ser Val Ile Pro Met Pro Gly Phe Ile Ala Gly Glu Pro Leu Pro Ser
5395 5400 5405

Ala Ile Glu Val Ala Val Arg Thr Gln Ala Glu Ala Val Leu Gln Glu
5410 5415 5420

Phe Ala Gly Gly Ser Phe Val Leu Val Gly His Ser Ser Gly Gly Trp
5425 5430 5435 5440

Leu Ala His Glu Val Ala Gly Glu Leu Glu Arg Arg Gly Val Val Pro
5445 5450 5455

Ala Gly Val Val Leu Leu Asp Thr Tyr Ile Pro Gly Glu Ile Thr Pro
5460 5465 5470

Arg Phe Ser Val Ala Met Ala His Arg Thr Tyr Glu Lys Leu Ala Thr
5475 5480 5485

Phe Thr Asp Met Gln Asp Val Gly Ile Thr Ala Met Gly Gly Tyr Phe
5490 5495 5500

Arg Met Phe Thr Glu Trp Thr Pro Thr Pro Ile Gly Ala Pro Thr Leu
5505 5510 5515 5520

Phe Val Arg Thr Glu Asp Cys Val Ala Asp Pro Glu Gly Arg Pro Trp
5525 5530 5535

Thr Asp Asp Ser Trp Arg Pro Gly Trp Thr Leu Ala Asp Ala Thr Val
5540 5545 5550

Gln Val Pro Gly Asp His Phe Ser Met Met Asp Glu His Ala Gly Ser
5555 5560 5565

BNSDOCID: <WO___9946387A1_I_>

Thr Ala Gln Ala Val Ala Ser Trp Leu Asp Lys Leu Asn Gln Arg Thr
5570 5575 5580

Ala Arg Gln Arg
5585

<210> 7
<211> 275
<212> PRT
<213> Saccharopolyspora spinosa

<400> 7
Val Leu Pro Gly Gly Ala Pro Thr Ser Gln Gln Val Gly Gln Met Tyr
1 5 10 15

Asp Leu Val Thr Pro Leu Leu Asn Ser Val Ala Gly Gly Pro Cys Ala
20 25 30

Ile His His Gly Tyr Trp Glu Asn Asp Gly Arg Ala Ser Trp Gln Gln
35 40 45

Ala Ala Asp Arg Leu Thr Asp Leu Val Ala Glu Arg Thr Val Leu Asp
50 55 60

Gly Gly Val Arg Leu Leu Asp Val Gly Cys Gly Thr Gly Gln Pro Ala
65 70 75 80

Leu Arg Val Ala Arg Asp Asn Ala Ile Gln Ile Thr Gly Ile Thr Val
85 90 95

Ser Gln Val Gln Val Ala Ile Ala Ala Asp Cys Ala Arg Glu Arg Gly
100 105 110

Leu Ser His Arg Val Asp Phe Ser Cys Val Asp Ala Met Ser Leu Pro
115 120 125

Tyr Pro Asp Asn Ala Phe Asp Ala Ala Trp Ala Met Gln Ser Leu Leu
130 135 140

Glu Met Ser Glu Pro Asp Arg Ala Ile Arg Glu Ile Leu Arg Val Leu
145 150 155 160

Lys Pro Gly Gly Ile Leu Gly Val Thr Glu Val Val Lys Arg Glu Ala
165 170 175

Gly Gly Gly Met Pro Val Ser Gly Asp Arg Trp Pro Thr Gly Leu Arg
180 185 190

Ile Cys Leu Ala Glu Gln Leu Leu Glu Ser Leu Arg Ala Ala Gly Phe
195 200 205

Glu Ile Leu Asp Trp Glu Asp Val Ser Ser Arg Thr Arg Tyr Phe Met
210 215 220

Pro Gln Phe Ala Glu Glu Leu Ala Ala His Gln His Gly Ile Ala Asp
225 230 235 240

BNSDOCID: <WO___9946387A1_I_>

```
Arg Tyr Gly Pro Ala Val Ala Gly Trp Ala Ala Ala Val Cys Asp Tyr
                245                 250                 255

Glu Lys Tyr Ala His Asp Met Gly Tyr Ala Ile Leu Thr Ala Arg Lys
            260                 265                 270

Pro Val Gly
        275
```

<210> 8
<211> 390
<212> PRT
<213> Saccharopolyspora spinosa

<400> 8

```
Met Arg Val Leu Val Val Pro Leu Pro Tyr Pro Thr His Leu Met Ala
  1               5                  10                  15

Met Val Pro Leu Cys Trp Ala Leu Gln Ala Ser Gly His Glu Val Leu
            20                  25                  30

Ile Ala Ala Pro Pro Glu Leu Gln Ala Thr Ala His Gly Ala Gly Leu
        35                  40                  45

Thr Thr Ala Gly Ile Arg Gly Asn Asp Arg Thr Gly Asp Thr Gly Gly
    50                  55                  60

Thr Thr Gln Leu Arg Phe Pro Asn Pro Ala Phe Gly Gln Arg Asp Thr
65                  70                  75                  80

Glu Ala Gly Arg Gln Leu Trp Glu Gln Thr Ala Ser Asn Val Ala Gln
                85                  90                  95

Ser Ser Leu Asp Gln Leu Pro Glu Tyr Leu Arg Leu Ala Glu Ala Trp
            100                 105                 110

Arg Pro Ser Val Leu Leu Val Asp Val Cys Ala Leu Ile Gly Arg Val
        115                 120                 125

Leu Gly Gly Leu Leu Asp Leu Pro Val Val Leu His Arg Trp Gly Val
    130                 135                 140

Asp Pro Thr Ala Gly Pro Phe Ser Asp Arg Ala His Glu Leu Leu Asp
145                 150                 155                 160

Pro Val Cys Arg His His Gly Leu Thr Gly Leu Pro Thr Pro Glu Leu
                165                 170                 175

Ile Leu Asp Pro Cys Pro Pro Ser Leu Gln Ala Ser Asp Ala Pro Gln
            180                 185                 190

Gly Ala Pro Val Gln Tyr Val Pro Tyr Asn Gly Ser Gly Ala Phe Pro
        195                 200                 205

Ala Trp Gly Ala Ala Arg Thr Ser Ala Arg Arg Val Cys Ile Cys Met
    210                 215                 220
```


BNSDOCID: <WO___9946387A1_I_>

```
Gly Arg Met Val Leu Asn Ala Thr Gly Pro Ala Pro Leu Leu Arg Ala
225                 230                 235                 240

Val Ala Ala Ala Thr Glu Leu Pro Gly Val Glu Ala Val Ile Ala Val
                245                 250                 255

Pro Pro Glu His Arg Ala Leu Leu Thr Asp Leu Pro Asp Asn Ala Arg
            260                 265                 270

Ile Ala Glu Ser Val Pro Leu Asn Leu Phe Leu Arg Thr Cys Glu Leu
        275                 280                 285

Val Ile Cys Ala Gly Gly Ser Gly Thr Ala Phe Thr Ala Thr Arg Leu
    290                 295                 300

Gly Ile Pro Gln Leu Val Leu Pro Gln Tyr Phe Asp Gln Phe Asp Tyr
305                 310                 315                 320

Ala Arg Asn Leu Ala Ala Ala Gly Ala Gly Ile Cys Leu Pro Asp Glu
                325                 330                 335

Gln Ala Gln Ser Asp His Glu Gln Phe Thr Asp Ser Ile Ala Thr Val
            340                 345                 350

Leu Gly Asp Thr Gly Phe Ala Ser Ala Ala Ile Lys Leu Ser Asp Glu
        355                 360                 365

Ile Thr Ala Met Pro His Pro Ala Ala Leu Val Arg Thr Leu Glu Asn
    370                 375                 380

Thr Ala Ala Ile Arg Ala
385                 390


<210> 9
<211> 250
<212> PRT
<213> Saccharopolyspora spinosa

<400> 9
Met Pro Ser Gln Asn Ala Leu Tyr Leu Asp Leu Leu Lys Lys Val Leu
  1                 5                  10                  15

Thr Asn Thr Ile Tyr Ser Asp Arg Pro His Pro Asn Ala Trp Gln Asp
            20                  25                  30

Asn Thr Asp Tyr Arg Gln Ala Ala Arg Ala Lys Gly Thr Asp Trp Pro
        35                  40                  45

Thr Val Ala His Thr Met Ile Gly Leu Glu Arg Leu Asp Asn Leu Gln
    50                  55                  60

His Cys Val Glu Ala Val Leu Ala Asp Gly Val Pro Gly Asp Phe Ala
65                  70                  75                  80

Glu Thr Gly Val Trp Arg Gly Gly Ala Cys Ile Phe Met Arg Ala Val
                85                  90                  95
```


BNSDOCID: <WO___9946387A1_I_>

```
Leu Gln Ala Phe Gly Asp Thr Gly Arg Thr Val Trp Val Val Asp Ser
            100                 105                 110

Phe Gln Gly Met Pro Glu Ser Ser Ala Gln Asp His Gln Ala Asp Gln
        115                 120                 125

Ala Met Ala Leu His Glu Tyr Asn Asp Val Leu Gly Val Ser Leu Glu
    130                 135                 140

Thr Val Arg Gln Asn Phe Ala Arg Tyr Gly Leu Leu Asp Glu Gln Val
145                 150                 155                 160

Arg Phe Leu Pro Gly Trp Phe Arg Asp Thr Leu Pro Thr Ala Pro Ile
                165                 170                 175

Gln Glu Leu Ala Val Leu Arg Leu Asp Gly Asp Leu Tyr Glu Ser Thr
            180                 185                 190

Met Asp Ser Leu Arg Asn Leu Tyr Pro Lys Leu Ser Pro Gly Gly Phe
        195                 200                 205

Val Ile Ile Asp Asp Tyr Phe Leu Pro Ser Cys Gln Asp Ala Val Lys
    210                 215                 220

Gly Phe Arg Ala Glu Leu Gly Ile Thr Glu Pro Ile His Asp Ile Asp
225                 230                 235                 240

Gly Thr Gly Ala Tyr Trp Arg Arg Ser Trp
                245                 250
```

<210> 10
<211> 395
<212> PRT
<213> Saccharopolyspora spinosa

<400> 10

```
Met Ser Glu Ile Ala Val Ala Pro Trp Ser Val Val Glu Arg Leu Leu
  1               5                  10                  15

Leu Ala Ala Gly Ala Gly Pro Ala Lys Leu Gln Glu Ala Val Gln Val
            20                  25                  30

Ala Gly Leu Asp Ala Val Ala Asp Ala Ile Val Asp Glu Leu Val Val
        35                  40                  45

Arg Cys Asp Pro Leu Ser Leu Asp Glu Ser Val Arg Ile Gly Leu Glu
    50                  55                  60

Ile Thr Ser Gly Ala Gln Leu Val Arg Arg Thr Val Glu Leu Asp His
65                  70                  75                  80

Ala Gly Leu Arg Leu Ala Ala Val Ala Glu Ala Ala Ala Val Leu Arg
                85                  90                  95

Phe Asp Ala Val Asp Leu Leu Glu Gly Leu Phe Gly Pro Val Asp Gly
            100                 105                 110
```


BNSDOCID: <WO___9946387A1_I_>

Arg Arg His Asn Ser Arg Glu Val Arg Trp Ser Asp Ser Met Thr Gln
115 120 125

Phe Ser Pro Asp Gln Gly Leu Ala Gly Ala Gln Arg Leu Leu Ala Phe
130 135 140

Arg Asn Arg Val Ser Thr Ala Val His Ala Val Leu Ala Ala Ala Ala
145 150 155 160

Thr Arg Arg Ala Asp Leu Gly Ala Leu Ala Val Arg Tyr Gly Ser Asp
165 170 175

Lys Trp Ala Asp Leu His Trp Tyr Thr Glu His Tyr Glu His His Phe
180 185 190

Ser Arg Phe Gln Asp Ala Pro Val Arg Val Leu Glu Ile Gly Ile Gly
195 200 205

Gly Tyr His Ala Pro Glu Leu Gly Gly Ala Ser Leu Arg Met Trp Gln
210 215 220

Arg Tyr Phe Arg Arg Gly Leu Val Tyr Gly Leu Asp Ile Phe Glu Lys
225 230 235 240

Ala Gly Asn Glu Gly His Arg Val Arg Lys Leu Arg Gly Asp Gln Ser
245 250 255

Asp Ala Glu Phe Leu Glu Asp Met Val Ala Lys Ile Gly Pro Phe Asp
260 265 270

Ile Val Ile Asp Asp Gly Ser His Val Asn Asp His Val Lys Lys Ser
275 280 285

Phe Gln Ser Leu Phe Pro His Val Arg Pro Gly Gly Leu Tyr Val Ile
290 295 300

Glu Asp Leu Gln Thr Ala Tyr Trp Pro Gly Tyr Gly Gly Arg Asp Gly
305 310 315 320

Glu Pro Ala Ala Gln Arg Thr Ser Ile Asp Met Leu Lys Glu Leu Ile
325 330 335

Asp Gly Leu His Tyr Gln Glu Arg Glu Ser Arg Cys Gly Thr Glu Pro
340 345 350

Ser Tyr Thr Glu Arg Asn Val Ala Ala Leu His Phe Tyr His Asn Leu
355 360 365

Val Phe Val Glu Lys Gly Leu Asn Ala Glu Thr Ala Ala Pro Gly Phe
370 375 380

Val Pro Arg Gln Ala Leu Gly Val Glu Gly Gly
385 390 395

<210> 11
<211> 539

BNSDOCID: <WO___9946387A1_I_>

<212> PRT
<213> Saccharopolyspora spinosa

<400> 11

```
Met Ile Ser Ala Ala Gly Glu Gln Ser Gly Pro Val Arg Lys Gly Gly
  1               5                  10                  15

Ala Val Pro Glu Phe His Asp Pro Ala Pro Met Asn Arg Arg Thr Pro
             20                  25                  30

Gly Thr Glu Ile Thr Val Glu Pro Asp Asp Pro Arg Tyr Pro Asp Leu
         35                  40                  45

Val Val Gly His Asn Pro Arg Phe Thr Gly Lys Pro Glu Arg Ile His
     50                  55                  60

Ile Ala Ser Ser Ala Glu Asp Val Val His Ala Val Ala Asp Ala Val
 65                  70                  75                  80

Arg Thr Gly Arg Arg Val Gly Val Arg Ser Gly Gly His Cys Phe Glu
                 85                  90                  95

Asn Leu Val Ala Asp Pro Ala Ile Arg Val Leu Val Asp Leu Ser Glu
            100                 105                 110

Leu Asn Arg Val Tyr Tyr Asp Ser Thr Arg Gly Ala Phe Ala Ile Glu
        115                 120                 125

Ala Gly Ala Ala Leu Gly Gln Val Tyr Arg Thr Leu Phe Lys Asn Trp
    130                 135                 140

Gly Val Thr Ile Pro Thr Gly Ala Cys Pro Gly Val Gly Ala Gly Gly
145                 150                 155                 160

His Ile Leu Gly Gly Gly Tyr Gly Pro Leu Ser Arg Arg Phe Gly Ser
                165                 170                 175

Val Val Asp Tyr Leu Gln Gly Val Glu Val Val Val Val Asp Gln Ala
            180                 185                 190

Gly Glu Val His Ile Val Glu Ala Asp Arg Asn Ser Thr Gly Ala Gly
        195                 200                 205

His Asp Leu Trp Trp Ala His Thr Gly Gly Gly Gly Gly Asn Phe Gly
    210                 215                 220

Ile Val Thr Arg Phe Trp Leu Arg Thr Pro Asp Val Val Ser Thr Asp
225                 230                 235                 240

Ala Ala Glu Leu Leu Pro Arg Pro Pro Ala Thr Val Leu Leu Arg Ser
                245                 250                 255

Phe His Trp Pro Trp His Glu Leu Thr Glu Gln Ser Phe Ala Val Leu
            260                 265                 270

Leu Gln Asn Phe Gly Asn Trp Tyr Glu Gln His Ser Ala Pro Glu Ser
        275                 280                 285
```


BNSDOCID: <WO___9946387A1_I_>

```
Thr Gln Leu Gly Leu Phe Ser Thr Leu Val Cys Ala His Arg Gln Ala
290                 295                 300

Gly Tyr Val Thr Leu Asn Val His Leu Asp Gly Thr Asp Pro Asn Ala
305                 310                 315                 320

Glu Arg Thr Leu Ala Glu His Leu Ser Ala Ile Asn Ala Gln Val Gly
                325                 330                 335

Val Thr Pro Ala Glu Gly Leu Arg Glu Thr Leu Pro Trp Leu Arg Ser
            340                 345                 350

Thr Gln Val Ala Gly Ala Ile Ala Glu Gly Gly Glu Pro Gly Met Gln
        355                 360                 365

Arg Thr Lys Val Lys Ala Ala Tyr Leu Arg Thr Gly Leu Ser Glu Ala
    370                 375                 380

Gln Leu Ala Thr Val Tyr Arg Arg Leu Thr Val Tyr Gly Tyr Asp Asn
385                 390                 395                 400

Pro Ala Ala Ala Leu Leu Leu Leu Gly Tyr Gly Gly Met Ala Asn Ala
                405                 410                 415

Val Ala Pro Ser Ala Thr Ala Leu Ala Gln Arg Asp Ser Val Leu Lys
            420                 425                 430

Ala Leu Phe Val Thr Asn Trp Ser Glu Pro Ala Glu Asp Glu Arg His
        435                 440                 445

Leu Thr Trp Ile Arg Gly Phe Tyr Arg Glu Met Tyr Ala Glu Thr Gly
    450                 455                 460

Gly Val Pro Val Pro Gly Thr Arg Val Asp Gly Ser Tyr Ile Asn Tyr
465                 470                 475                 480

Pro Asp Thr Asp Leu Ala Asp Pro Leu Trp Asn Thr Ser Gly Val Ala
                485                 490                 495

Trp His Asp Leu Tyr Tyr Lys Asp Asn Tyr Pro Arg Leu Gln Arg Ala
            500                 505                 510

Lys Ala Arg Trp Asp Pro Gln Asn Ile Phe Gln His Gly Leu Ser Ile
        515                 520                 525

Lys Pro Pro Ala Arg Leu Ser Pro Gly Gln Pro
    530                 535
```

<210> 12
<211> 397
<212> PRT
<213> Saccharopolyspora spinosa

<400> 12

```
Met Ser Thr Thr His Glu Ile Glu Thr Val Glu Arg Ile Ile Leu Ala
 1               5                  10                  15
```


BNSDOCID: <WO___9946387A1_I_>

```
Ala Gly Ser Ser Ala Ala Ser Leu Ala Asp Leu Thr Thr Glu Leu Gly
              20                  25                  30

Leu Ala Arg Ile Ala Pro Val Leu Ile Asp Glu Ile Leu Phe Arg Ala
          35                  40                  45

Glu Pro Ala Pro Asp Ile Glu Arg Thr Glu Val Ala Val Gln Ile Thr
      50                  55                  60

His Arg Gly Glu Thr Val Asp Phe Val Leu Thr Leu Gln Ser Gly Glu
 65                  70                  75                  80

Leu Ile Lys Ala Glu Gln Arg Pro Val Gly Asp Val Pro Leu Arg Ile
                 85                  90                  95

Gly Tyr Glu Leu Thr Asp Leu Ile Ala Glu Leu Phe Gly Pro Gly Ala
            100                 105                 110

Pro Arg Ala Val Gly Ala Arg Ser Thr Asn Phe Leu Arg Thr Thr Thr
        115                 120                 125

Ser Gly Ser Ile Pro Gly Pro Ser Glu Leu Ser Asp Gly Phe Gln Ala
    130                 135                 140

Ile Ser Ala Val Val Ala Gly Cys Gly His Arg Arg Pro Asp Leu Asn
145                 150                 155                 160

Leu Leu Ala Ser His Tyr Arg Thr Asp Lys Trp Gly Gly Leu His Trp
                165                 170                 175

Phe Thr Pro Leu Tyr Glu Arg His Leu Gly Glu Phe Arg Asp Arg Pro
            180                 185                 190

Val Arg Ile Leu Glu Ile Gly Val Gly Gly Tyr Asn Phe Asp Gly Gly
        195                 200                 205

Gly Gly Glu Ser Leu Lys Met Trp Lys Arg Tyr Phe His Arg Gly Leu
    210                 215                 220

Val Phe Gly Met Asp Val Phe Asp Lys Ser Phe Leu Asp Gln Gln Arg
225                 230                 235                 240

Leu Cys Thr Val Arg Ala Asp Gln Ser Lys Pro Glu Glu Leu Ala Ala
                245                 250                 255

Val Asp Asp Lys Tyr Gly Pro Phe Asp Ile Ile Ile Asp Asp Gly Ser
            260                 265                 270

His Ile Asn Gly His Val Arg Thr Ser Leu Glu Thr Leu Phe Pro Arg
        275                 280                 285

Leu Arg Ser Gly Gly Val Tyr Val Ile Glu Asp Leu Trp Thr Thr Tyr
    290                 295                 300

Ala Pro Gly Phe Gly Gly Gln Ala Gln Cys Pro Ala Ala Pro Gly Thr
305                 310                 315                 320

Thr Val Ser Leu Leu Lys Asn Leu Leu Glu Gly Val Gln His Glu Glu
```


BNSDOCID: <WO___9946387A1_I_>

325 330 335

Gln Pro His Ala Gly Ser Tyr Glu Pro Ser Tyr Leu Glu Arg Asn Leu
340 345 350

Val Gly Leu His Thr Tyr His Asn Ile Ala Phe Leu Glu Lys Gly Val
355 360 365

Asn Ala Glu Gly Gly Val Pro Ala Trp Val Pro Arg Ser Leu Asp Asp
370 375 380

Ile Leu His Leu Ala Asp Val Asn Ser Ala Glu Asp Glu
385 390 395

<210> 13
<211> 283
<212> PRT
<213> Saccharopolyspora spinosa

<400> 13
Val Glu Ser Ile Phe Asp Ala Leu Ala His Gly Arg Pro Leu His His
1 5 10 15

Gly Tyr Trp Ala Gly Gly Tyr Arg Glu Asp Ala Gly Ala Thr Pro Trp
20 25 30

Ser Asp Ala Ala Asp Gln Leu Thr Asp Leu Phe Ile Asp Lys Ala Ala
35 40 45

Leu Arg Pro Gly Ala His Leu Phe Asp Leu Gly Cys Gly Asn Gly Gln
50 55 60

Pro Val Val Arg Ala Ala Cys Ala Ser Gly Val Arg Val Thr Gly Ile
65 70 75 80

Thr Val Asn Ala Gln His Leu Ala Ala Ala Thr Arg Leu Ala Asn Glu
85 90 95

Thr Gly Leu Ala Gly Ser Leu Glu Phe Asp Leu Val Asp Gly Ala Gln
100 105 110

Leu Pro Tyr Pro Asp Gly Phe Phe Gln Ala Ala Trp Ala Met Gln Ser
115 120 125

Val Val Gln Ile Val Asp Gln Ala Ala Ala Ile Arg Glu Val His Arg
130 135 140

Ile Leu Glu Pro Gly Gly Arg Phe Val Leu Gly Asp Ile Ile Thr Arg
145 150 155 160

Val Arg Leu Pro Glu Glu Tyr Ala Ala Val Trp Thr Gly Thr Thr Ala
165 170 175

His Thr Leu Asn Ser Phe Thr Ala Leu Val Ser Glu Ala Gly Phe Glu
180 185 190

Ile Leu Glu Val Thr Asp Leu Thr Ala Gln Thr Arg Cys Met Val Ser

BNSDOCID: <WO___9946387A1_I_>

195 200 205

Trp Tyr Val Asp Glu Leu Leu Arg Lys Leu Asp Glu Leu Ala Gly Val
210 215 220

Glu Pro Ala Ala Val Gly Thr Tyr Gln Gln Arg Tyr Leu Gly Asp Ile
225 230 235 240

Ala Ala Lys His Gly Pro Gly Pro Ala Gln Leu Ile Ala Ala Val Ala
245 250 255

Glu Tyr Arg Lys His Pro Asp Tyr Ala Arg Asn Glu Glu Ser Met Gly
260 265 270

Phe Met Leu Leu Gln Ala Arg Lys Lys Gln Ser
275 280

<210> 14
<211> 320
<212> PRT
<213> Saccharopolyspora spinosa

<400> 14
Met Pro Asn Ala Val Ser Gly Thr Val Leu Val Pro Asn Ile Pro Trp
1 5 10 15

Pro Arg Glu Asp Arg Pro Ile Ile Thr Phe Ala Val Gly Thr His Gly
20 25 30

Leu Gly Ser Gln Val Ala Pro Ser Tyr Leu Leu Arg Thr Gly Thr Glu
35 40 45

Pro Glu Thr Glu Leu Ile Ala Val Ala Leu Asp Arg Gly Trp Ala Val
50 55 60

Val Ile Thr Asp Tyr Glu Gly Leu Gly Thr Pro Gly Thr His Thr Tyr
65 70 75 80

Thr Val Gly Arg Ala Gln Gly His Ala Met Leu Asp Ala Ala Arg Ala
85 90 95

Ala Gln Arg Leu Pro Gly Ser Gly Leu Thr Thr Asp Cys Pro Val Gly
100 105 110

Ile Trp Gly Tyr Ala Gln Gly Gly Gln Ala Ser Ala Phe Ala Gly Glu
115 120 125

Leu His Pro Thr Tyr Ala Pro Glu Leu Arg Ile Arg Ala Ala Ala Ala
130 135 140

Gly Ala Val Pro Ile Asp Leu Leu Asp Ile Ile His Arg Asn Asp Gly
145 150 155 160

Val Phe Thr Gly Pro Val Leu Ala Gly Leu Val Gly His Ala Ala Ala
165 170 175

Tyr Pro Asp Leu Pro Phe Asp Glu Leu Leu Thr Glu Ala Gly Arg Thr

BNSDOCID: <WO___9946387A1_I_>

180 185 190

Ala Val Asp Gln Val Arg Glu Leu Gly Ala Pro Glu Leu Val Thr Arg
195 200 205

Phe Leu Gly Arg Glu Leu Ser Asp Phe Leu Asp Thr Ser Gly Leu Phe
210 215 220

Glu Gln Pro Arg Trp Arg Ala Arg Leu Ala Glu Ser Val Ala Gly Arg
225 230 235 240

Asn Gly Gly Pro Val Val Pro Thr Leu Val Tyr His Ser Thr Asp Asp
245 250 255

Glu Ile Val Pro Phe Ala Phe Gly Glu Arg Leu Arg Asp Ser Tyr Arg
260 265 270

Ala Ala Gly Thr Pro Val Arg Trp His Pro Leu Ser Gly Leu Ala His
275 280 285

Phe Pro Ala Ala Leu Ala Ser Ser Arg Val Val Val Ser Trp Phe Asp
290 295 300

Glu His Phe Ser Glu Pro Ser Ala Ile Ser Gly Pro Arg Asp Ala Arg
305 310 315 320

<210> 15
<211> 332
<212> PRT
<213> Saccharopolyspora spinosa

<400> 15
Met Arg Lys Pro Val Arg Ile Gly Val Leu Gly Cys Ala Ser Phe Ala
1 5 10 15

Trp Arg Arg Met Leu Pro Ala Met Cys Asp Val Ala Glu Thr Glu Val
20 25 30

Val Ala Val Ala Ser Arg Asp Pro Ala Lys Ala Glu Arg Phe Ala Ala
35 40 45

Arg Phe Glu Cys Glu Ala Val Leu Gly Tyr Gln Arg Leu Leu Glu Arg
50 55 60

Pro Asp Ile Asp Ala Val Tyr Val Pro Leu Pro Pro Gly Met His Ala
65 70 75 80

Glu Trp Ile Gly Lys Ala Leu Glu Ala Asp Lys His Val Leu Ala Glu
85 90 95

Lys Pro Leu Thr Thr Thr Ala Ser Asp Thr Ala Arg Leu Val Gly Leu
100 105 110

Ala Arg Arg Lys Asn Leu Leu Leu Arg Glu Asn Tyr Leu Phe Leu His

BNSDOCID: <WO___9946387A1_I_>

```
        115                 120                 125

His Gly Arg His Asp Val Val Arg Asp Leu Leu Gln Ser Gly Glu Ile
    130                 135                 140

Gly Glu Leu Arg Glu Phe Thr Ala Val Phe Gly Ile Pro Pro Leu Pro
145                 150                 155                 160

Asp Thr Asp Ile Arg Tyr Arg Thr Glu Leu Gly Gly Gly Ala Leu Leu
                165                 170                 175

Asp Ile Gly Val Tyr Pro Ala Arg Ala Ala Arg His Phe Leu Leu Gly
            180                 185                 190

Pro Leu Thr Val Leu Gly Ala Ser Ser His Glu Ala Gln Glu Ser Gly
        195                 200                 205

Val Asp Leu Ser Gly Ser Val Leu Leu Gln Ser Glu Gly Gly Thr Val
    210                 215                 220

Ala His Leu Gly Tyr Gly Phe Val His His Tyr Arg Ser Ala Tyr Glu
225                 230                 235                 240

Leu Trp Gly Ser Arg Gly Arg Ile Val Val Asp Arg Ala Phe Thr Pro
                245                 250                 255

Pro Ala Glu Trp Gln Ala Val Ile Arg Ile Glu Arg Lys Gly Val Val
            260                 265                 270

Asp Glu Leu Ser Leu Pro Ala Glu Asp Gln Val Arg Lys Ala Val Thr
        275                 280                 285

Ala Phe Ala Arg Asp Ile Arg Ala Gly Thr Gly Val Asp Asp Pro Ala
    290                 295                 300

Val Ala Gly Asp Ser Gly Glu Ser Met Ile Gln Gln Ala Ala Leu Val
305                 310                 315                 320

Glu Ala Ile Gly Gln Ala Arg Arg Cys Gly Ser Thr
                325                 330
```

<210> 16
<211> 486
<212> PRT
<213> Saccharopolyspora spinosa

<400> 16

```
Met Ser Ser Ser Val Glu Ala Glu Ala Ser Ala Ala Ala Pro Leu Gly
  1               5                  10                  15

Ser Asn Asn Thr Arg Arg Phe Val Asp Ser Ala Leu Ser Ala Cys Asn
             20                  25                  30

Gly Met Ile Pro Thr Thr Glu Phe His Cys Trp Leu Ala Asp Arg Leu
         35                  40                  45

Gly Glu Asn Ser Phe Glu Thr Asn Arg Ile Pro Phe Asp Arg Leu Ser
```


BNSDOCID: <WO___9946387A1_I_>

50 55 60

Lys Trp Lys Phe Asp Ala Ser Thr Glu Asn Leu Val His Ala Asp Gly
65 70 75 80

Arg Phe Phe Thr Val Glu Gly Leu Gln Val Glu Thr Asn Tyr Gly Ala
85 90 95

Ala Pro Ser Trp His Gln Pro Ile Ile Asn Gln Ala Glu Val Gly Ile
100 105 110

Leu Gly Ile Leu Val Lys Glu Ile Asp Gly Val Leu His Cys Leu Met
115 120 125

Ser Ala Lys Met Glu Pro Gly Asn Val Asn Val Leu Gln Leu Ser Pro
130 135 140

Thr Val Gln Ala Thr Arg Ser Asn Tyr Thr Gln Ala His Arg Gly Ser
145 150 155 160

Val Pro Pro Tyr Val Asp Tyr Phe Leu Gly Arg Gly Arg Gly Arg Val
165 170 175

Leu Val Asp Val Leu Gln Ser Glu Gln Gly Ser Trp Phe Tyr Arg Lys
180 185 190

Arg Asn Arg Asn Met Val Val Glu Val Gln Glu Glu Val Pro Val Leu
195 200 205

Pro Asp Phe Cys Trp Leu Thr Leu Gly Gln Val Leu Ala Leu Leu Arg
210 215 220

Gln Asp Asn Ile Val Asn Met Asp Thr Arg Thr Val Leu Ser Cys Ile
225 230 235 240

Pro Phe His Asp Ser Ala Thr Gly Pro Glu Leu Ala Ala Ser Glu Glu
245 250 255

Pro Phe Arg Gln Ala Val Ala Arg Ser Leu Ser His Gly Ile Asp Ser
260 265 270

Ser Ser Ile Ser Glu Ala Val Gly Trp Phe Glu Glu Ala Lys Ala Arg
275 280 285

Tyr Arg Leu Arg Ala Thr Arg Val Pro Leu Ser Arg Val Asp Lys Trp
290 295 300

Tyr Arg Thr Asp Thr Glu Ile Ala His Gln Asp Gly Lys Tyr Phe Ala
305 310 315 320

Val Ile Ala Val Ser Val Ser Ala Thr Asn Arg Glu Val Ala Ser Trp
325 330 335

Thr Gln Pro Met Ile Glu Pro Arg Glu Gln Gly Glu Ile Ala Leu Leu
340 345 350

Val Lys Arg Ile Gly Gly Val Leu His Gly Leu Val His Ala Arg Val
355 360 365

BNSDOCID: <WO___9946387A1_I_>

```
Glu Ala Gly Tyr Lys Trp Thr Ala Glu Ile Ala Pro Thr Val Gln Cys
    370                 375                 380

Ser Val Ala Asn Tyr Gln Ser Thr Pro Ser Asn Asp Trp Pro Pro Phe
385                 390                 395                 400

Leu Asp Asp Val Leu Thr Ala Asp Pro Glu Thr Val Arg Tyr Glu Ser
                405                 410                 415

Ile Leu Ser Glu Glu Gly Gly Arg Phe Tyr Gln Ala Gln Asn Arg Tyr
            420                 425                 430

Arg Ile Ile Glu Val His Glu Asp Phe Ala Ala Arg Pro Pro Ser Asp
        435                 440                 445

Phe Arg Trp Met Thr Leu Gly Gln Leu Gly Glu Leu Leu Arg Ser Thr
    450                 455                 460

His Phe Leu Asn Ile Gln Ala Arg Ser Leu Val Ala Ser Leu His Ser
465                 470                 475                 480

Leu Trp Ala Leu Gly Arg
                485
```

<210> 17
<211> 455
<212> PRT
<213> Saccharopolyspora spinosa

<400> 17

```
Val Ile Leu Gly Met Leu Pro Gly Cys Ser Ile Ala Ile Gly Glu Phe
  1               5                  10                  15

Met Arg Val Leu Phe Thr Pro Leu Pro Ala Ser Ser His Phe Phe Asn
            20                  25                  30

Leu Val Pro Leu Ala Trp Ala Leu Arg Ala Ala Gly His Glu Val Arg
        35                  40                  45

Val Ala Ile Cys Pro Asn Met Val Ser Met Val Thr Gly Ala Gly Leu
    50                  55                  60

Thr Ala Val Pro Val Gly Asp Glu Leu Asp Leu Ile Ser Leu Ala Ala
65                  70                  75                  80

Lys Asn Glu Leu Val Leu Gly Ser Gly Val Ser Phe Asp Glu Lys Gly
                85                  90                  95

Arg His Pro Glu Leu Phe Asp Glu Leu Leu Ser Ile Asn Ser Gly Arg
            100                 105                 110

Asp Thr Asp Ala Val Glu Gln Leu His Leu Val Asp Asp Arg Ser Leu
        115                 120                 125

Asp Asp Leu Met Gly Phe Ala Glu Lys Trp Gln Pro Asp Leu Val Val
    130                 135                 140
```


BNSDOCID: <WO___9946387A1_I_>

Trp Asp Ala Met Val Cys Ser Gly Pro Val Val Ala Arg Ala Leu Gly
145 150 155 160

Ala Arg His Val Arg Met Leu Val Ala Leu Asp Val Ser Gly Trp Leu
165 170 175

Arg Ser Gly Phe Leu Glu Tyr Gln Glu Ser Lys Pro Pro Glu Gln Arg
180 185 190

Val Asp Pro Leu Gly Thr Trp Leu Gly Ala Lys Leu Ala Lys Phe Gly
195 200 205

Ala Thr Phe Asp Glu Glu Ile Val Thr Gly Gln Ala Thr Ile Asp Pro
210 215 220

Ile Pro Ser Trp Met Arg Leu Pro Val Asp Leu Asp Tyr Ile Ser Met
225 230 235 240

Arg Phe Val Pro Tyr Asn Gly Pro Ala Val Leu Pro Glu Trp Leu Arg
245 250 255

Glu Arg Pro Thr Lys Pro Arg Val Cys Ile Thr Arg Gly Leu Thr Lys
260 265 270

Arg Arg Leu Ser Arg Val Thr Glu Gln Tyr Gly Glu Gln Ser Asp Gln
275 280 285

Glu Gln Ala Met Val Glu Arg Leu Leu Arg Gly Ala Ala Arg Leu Asp
290 295 300

Val Glu Val Ile Ala Thr Leu Ser Asp Asp Glu Val Arg Glu Met Gly
305 310 315 320

Glu Leu Pro Ser Asn Val Arg Val His Glu Tyr Val Pro Leu Asn Glu
325 330 335

Leu Leu Glu Ser Cys Ser Val Ile Ile His His Gly Ser Thr Thr Thr
340 345 350

Gln Glu Thr Ala Thr Val Asn Gly Val Pro Gln Leu Ile Leu Pro Gly
355 360 365

Thr Phe Trp Asp Glu Ser Arg Arg Ala Glu Leu Leu Ala Asp Arg Gly
370 375 380

Ala Gly Leu Val Leu Asp Pro Ala Thr Phe Thr Glu Asp Asp Val Arg
385 390 395 400

Gly Gln Leu Ala Arg Leu Leu Asp Glu Pro Ser Phe Ala Ala Asn Ala
405 410 415

Ala Leu Ile Arg Arg Glu Ile Glu Glu Ser Pro Ser Pro His Asp Ile
420 425 430

Val Pro Arg Leu Glu Lys Leu Val Ala Glu Arg Glu Asn Arg Arg Thr
435 440 445

BNSDOCID: <WO___9946387A1_I_>

```
Gly Gln Ser Asp Gly His Pro
    450                 455


<210> 18
<211> 462
<212> PRT
<213> Saccharopolyspora spinosa

<400> 18
Met Gln Ser Arg Lys Thr Arg Ala Leu Gly Lys Gly Arg Ala Arg Val
  1               5                  10                  15

Thr Ser Cys Asp Asp Thr Cys Ala Thr Ala Thr Glu Met Val Pro Asp
             20                  25                  30

Ala Lys Asp Arg Ile Leu Ala Ser Val Arg Asp Tyr His Arg Glu Gln
         35                  40                  45

Glu Ser Pro Thr Phe Val Ala Gly Ser Thr Pro Ile Arg Pro Ser Gly
     50                  55                  60

Ala Val Leu Asp Glu Asp Asp Arg Val Ala Leu Val Glu Ala Ala Leu
 65                  70                  75                  80

Glu Leu Arg Ile Ala Ala Gly Gly Asn Ala Arg Arg Phe Glu Ser Glu
                 85                  90                  95

Phe Ala Arg Phe Phe Gly Leu Arg Lys Ala His Leu Val Asn Ser Gly
            100                 105                 110

Ser Ser Ala Asn Leu Leu Ala Leu Ser Ser Leu Thr Ser Pro Lys Leu
        115                 120                 125

Gly Glu Ala Arg Leu Arg Pro Gly Asp Glu Val Ile Thr Ala Ala Val
    130                 135                 140

Gly Phe Pro Thr Thr Ile Asn Pro Ala Val Gln Asn Gly Leu Val Pro
145                 150                 155                 160

Val Phe Val Asp Val Glu Leu Gly Thr Tyr Asn Ala Thr Pro Asp Arg
                165                 170                 175

Ile Lys Ala Ala Val Thr Glu Arg Thr Arg Ala Ile Met Leu Ala His
            180                 185                 190

Thr Leu Gly Asn Pro Phe Ala Ala Asp Glu Ile Ala Glu Ile Ala Lys
        195                 200                 205

Glu His Glu Leu Phe Leu Val Glu Asp Asn Cys Asp Ala Val Gly Ser
    210                 215                 220

Thr Tyr Arg Gly Arg Leu Thr Gly Thr Phe Gly Asp Leu Thr Thr Val
225                 230                 235                 240

Ser Phe Tyr Pro Ala His His Ile Thr Ser Gly Glu Gly Gly Cys Val
                245                 250                 255
```


BNSDOCID: <WO___9946387A1_I_>

```
Leu Thr Gly Ser Leu Glu Leu Ala Arg Ile Ile Glu Ser Leu Arg Asp
            260                 265                 270

Trp Gly Arg Asp Cys Trp Cys Glu Pro Gly Val Asp Asn Thr Cys Arg
        275                 280                 285

Lys Arg Phe Asp Tyr His Leu Gly Thr Leu Pro Pro Gly Tyr Asp His
    290                 295                 300

Lys Tyr Thr Phe Ser His Val Gly Tyr Asn Leu Lys Thr Thr Asp Leu
305                 310                 315                 320

Gln Ala Ala Leu Ala Leu Ser Gln Leu Ser Lys Ile Ser Ala Phe Gly
                325                 330                 335

Ser Ala Arg Arg Arg Asn Trp Arg Arg Leu Arg Glu Gly Leu Ser Gly
            340                 345                 350

Leu Pro Gly Leu Leu Leu Pro Val Ala Thr Pro His Ser Asp Pro Ser
        355                 360                 365

Trp Phe Gly Phe Ala Ile Thr Ile Ser Ala Asp Ala Gly Phe Thr Arg
    370                 375                 380

Ala Ala Leu Val Asn Phe Leu Glu Ser Arg Asn Ile Gly Thr Arg Leu
385                 390                 395                 400

Leu Phe Gly Gly Asn Ile Thr Arg His Pro Ala Phe Glu Gln Val Arg
                405                 410                 415

Tyr Arg Ile Ala Asp Ala Leu Thr Asn Ser Asp Ile Val Thr Asp Arg
            420                 425                 430

Thr Phe Trp Val Gly Val Tyr Pro Gly Ile Thr Asp Gln Met Ile Asp
        435                 440                 445

Tyr Val Val Glu Ser Ile Ala Glu Phe Val Ala Lys Ser Ser
    450                 455                 460


<210> 19
<211> 385
<212> PRT
<213> Saccharopolyspora spinosa

<400> 19
Val Ile Asn Leu His Gln Pro Ile Leu Gly Thr Glu Glu Leu Asp Ala
  1               5                  10                  15

Ile Ala Glu Val Phe Ala Ser Asn Trp Ile Gly Leu Gly Pro Arg Thr
            20                  25                  30

Arg Thr Phe Glu Ala Glu Phe Ala His His Leu Gly Val Asp Pro Glu
        35                  40                  45

Gln Val Val Phe Leu Asn Ser Gly Thr Ala Ala Leu Phe Leu Thr Val
    50                  55                  60
```


BNSDOCID: <WO___9946387A1_I_>

```
Gln Val Leu Asp Leu Gly Pro Gly Asp Asp Val Val Leu Pro Ser Ile
 65                  70                  75                  80

Ser Phe Val Ala Ala Ala Asn Ala Ile Ala Ser Ser Gly Ala Arg Pro
                 85                  90                  95

Val Phe Cys Asp Val Asp Pro Arg Thr Leu Asn Pro Thr Leu Asp Asp
            100                 105                 110

Val Ala Arg Ala Ile Thr Pro Ala Thr Lys Ala Val Leu Leu Leu His
        115                 120                 125

Tyr Gly Gly Ser Pro Gly Glu Val Thr Ala Ile Ala Asp Phe Cys Arg
    130                 135                 140

Glu Lys Gly Leu Met Leu Ile Glu Asp Ser Ala Cys Ala Val Ala Ser
145                 150                 155                 160

Ser Val His Gly Thr Ala Cys Gly Thr Phe Gly Asp Leu Ala Thr Trp
                165                 170                 175

Ser Phe Asp Ala Met Lys Ile Leu Val Thr Gly Asp Gly Gly Met Phe
            180                 185                 190

Tyr Ala Ala Asp Pro Glu Leu Ala His Arg Ala Arg Arg Leu Ala Tyr
        195                 200                 205

His Gly Leu Glu Gln Met Ser Gly Phe Asp Ser Ala Lys Ser Ser Asn
    210                 215                 220

Arg Trp Trp Asp Ile Arg Val Glu Asp Ile Gly Gln Arg Leu Ile Gly
225                 230                 235                 240

Asn Asp Met Thr Ala Ala Leu Gly Ser Val Gln Leu Arg Lys Leu Pro
                245                 250                 255

Glu Phe Ile Asn Arg Arg Arg Glu Ile Ala Thr Gln Tyr Asp Arg Leu
            260                 265                 270

Leu Ser Asp Val Pro Gly Val Leu Leu Pro Pro Thr Leu Pro Asp Gly
        275                 280                 285

His Val Ser Ser His Tyr Phe Tyr Trp Val Gln Leu Ala Pro Glu Ile
    290                 295                 300

Arg Asp Gln Val Ala Gln Gln Met Leu Glu Arg Gly Ile Tyr Thr Ser
305                 310                 315                 320

Tyr Arg Tyr Pro Pro Leu His Lys Val Pro Ile Tyr Arg Ala Asp Cys
                325                 330                 335

Lys Leu Pro Ser Ala Glu Asp Ala Cys Arg Arg Thr Leu Leu Leu Pro
            340                 345                 350

Leu His Pro Ser Leu Asp Asp Ala Glu Val Arg Thr Val Ala Asp Glu
        355                 360                 365

Phe Gln Lys Ala Val Glu His His Ile Ser Gln Arg Ser Pro Leu Arg
```


BNSDOCID: <WO___9946387A1_I_>

370 375 380

Lys
385

<210> 20
<211> 249
<212> PRT
<213> Saccharopolyspora spinosa

<400> 20
Met Ser Arg Val Ser Asp Thr Phe Ala Glu Thr Ser Ser Val Tyr Ser
1 5 10 15

Pro Asp His Ala Asp Ile Tyr Asp Ala Ile His Ser Ala Arg Gly Arg
20 25 30

Asp Trp Ala Ala Glu Ala Gly Glu Val Val Gln Leu Val Arg Thr Arg
35 40 45

Leu Pro Glu Ala Gln Ser Leu Leu Asp Val Ala Cys Gly Thr Gly Ala
50 55 60

His Leu Glu Arg Phe Arg Ala Glu Tyr Ala Lys Val Ala Gly Leu Glu
65 70 75 80

Leu Ser Asp Ala Met Arg Glu Ile Ala Ile Arg Arg Val Pro Glu Val
85 90 95

Pro Ile His Ile Gly Asp Ile Arg Asp Phe Asp Leu Gly Glu Pro Phe
100 105 110

Asp Val Ile Thr Cys Leu Cys Phe Thr Ala Ala Tyr Met Arg Thr Val
115 120 125

Asp Asp Leu Arg Arg Val Thr Arg Asn Met Ala Arg His Leu Ala Pro
130 135 140

Gly Gly Val Ala Val Ile Glu Pro Trp Trp Phe Pro Asp Lys Phe Ile
145 150 155 160

Asp Gly Phe Val Thr Gly Ala Val Ala His His Gly Glu Arg Val Ile
165 170 175

Ser Arg Leu Ser His Ser Val Leu Glu Gly Arg Thr Ser Arg Met Thr
180 185 190

Val Arg Tyr Thr Val Ala Glu Pro Thr Gly Ile Arg Asp Phe Thr Glu
195 200 205

Phe Glu Ile Leu Ser Leu Phe Thr Glu Asp Glu Tyr Thr Ala Ala Leu
210 215 220

Glu Asp Ala Gly Ile Arg Ala Glu Tyr Leu Pro Gly Ala Pro Asn Gly
225 230 235 240

Arg Gly Leu Phe Val Gly Ile Arg Asn

BNSDOCID: <WO___9946387A1_I_>

245

<210> 21
<211> 255
<212> PRT
<213> Saccharopolyspora spinosa

<400> 21

```
Met Val Leu Val Pro Arg Arg Phe Arg Ala Thr Leu Glu Ser Met Ser
  1               5                  10                  15

Glu Gln Thr Ile Ala Leu Val Thr Gly Ala Asn Lys Gly Ile Gly Tyr
             20                  25                  30

Glu Ile Ala Ala Gly Leu Gly Ala Leu Gly Trp Ser Val Gly Ile Gly
         35                  40                  45

Ala Arg Asp His Gln Arg Gly Glu Asp Ala Val Ala Lys Leu Arg Ala
     50                  55                  60

Asp Gly Val Asp Ala Phe Ala Val Ser Leu Asp Val Thr Asp Asp Ala
 65                  70                  75                  80

Ser Val Ala Ala Ala Ala Ala Leu Leu Glu Glu Arg Ala Gly Arg Leu
                 85                  90                  95

Asp Val Leu Val Asn Asn Ala Gly Ile Ala Gly Ala Trp Pro Glu Glu
            100                 105                 110

Pro Ser Thr Val Thr Pro Ala Ser Leu Arg Ala Val Val Glu Thr Asn
        115                 120                 125

Val Ile Gly Val Val Arg Val Thr Asn Ala Met Leu Pro Leu Leu Arg
    130                 135                 140

Arg Ser Glu Arg Pro Arg Ile Val Asn Gln Ser Ser His Val Ala Ser
145                 150                 155                 160

Leu Thr Leu Gln Thr Thr Pro Gly Val Asp Leu Gly Gly Ile Ser Gly
                165                 170                 175

Ala Tyr Ser Pro Ser Lys Thr Phe Leu Asn Ala Ile Thr Ile Gln Tyr
            180                 185                 190

Ala Lys Glu Leu Ser Asp Thr Asn Ile Lys Ile Asn Asn Ala Cys Pro
        195                 200                 205

Gly Tyr Val Ala Thr Asp Leu Asn Gly Phe His Gly Thr Ser Thr Pro
    210                 215                 220

Ala Asp Gly Ala Arg Ile Ala Ile Arg Leu Ala Thr Leu Pro Asp Asp
225                 230                 235                 240

Gly Pro Thr Gly Gly Met Phe Asp Asp Ala Gly Asn Val Pro Trp
                245                 250                 255
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BNSDOCID: <WO___9946387A1_I_>

<210> 22
<211> 278
<212> PRT
<213> Saccharopolyspora spinosa

<400> 22
Met Glu Thr Arg Glu Leu Arg Tyr Phe Val Ala Val Ala Glu Glu Leu
1 5 10 15

His Phe Gly Arg Ala Ala Gln Arg Leu Gly Ile Ala Gln Pro Pro Leu
20 25 30

Ser Arg Thr Ile Ala Gln Leu Glu Gln Arg Leu Gly Val Val Leu Leu
35 40 45

Gln Arg Thr Ser Arg Lys Val Ser Leu Thr Glu Ala Gly Ala Met Leu
50 55 60

Leu Thr Glu Gly Arg Ala Ile Leu Gly Ala Leu Ala Ala Ala Glu Arg
65 70 75 80

Arg Thr Gln Arg Ala Ala Thr Ser Gln Pro Ser Leu Val Leu Ala Ala
85 90 95

Lys Ala Gly Ala Ser Gly Glu Leu Leu Ala Lys Leu Leu Asp Ala Tyr
100 105 110

Ala Ala Glu Pro Gly Ala Val Ala Val Asp Leu Leu Leu Cys Glu Ser
115 120 125

Gln Pro Gln Lys Thr Leu His Asp Gly Arg Ala Asp Val Ala Leu Leu
130 135 140

His Gln Pro Phe Asp Pro Thr Ala Glu Leu Asp Ile Glu Ile Leu Asn
145 150 155 160

Thr Glu Gln Gln Val Ala Ile Leu Pro Thr Ser His Pro Leu Ala Ser
165 170 175

Glu Pro His Val Arg Met Ala Asp Val Ser Ser Leu Pro Asp Leu Pro
180 185 190

Leu Ala Arg Trp Pro Gly Pro Asp Gly Val Tyr Pro Asp Gly Pro Gly
195 200 205

Val Glu Val Arg Asn Gln Thr Gln Leu Phe Gln Met Ile Ala Leu Gly
210 215 220

Arg Thr Thr Val Val Met Pro Glu Ser Ser Arg Val Asn Leu Leu Glu
225 230 235 240

Gly Leu Ala Ala Val Pro Val Leu Asp Ala Pro Asp Val Thr Thr Val
245 250 255

Ile Ala Trp Pro Pro His Ser Arg Ser Arg Ala Leu Ala Gly Leu Val
260 265 270

Arg Val Ala Thr Leu Leu

BNSDOCID: <WO___9946387A1_I_>

275

<210> 23
<211> 198
<212> PRT
<213> Saccharopolyspora spinosa

<400> 23
Met Met Leu Lys Arg His Arg Leu Thr Thr Ala Ile Thr Gly Leu Leu
1 5 10 15

Gly Gly Val Leu Leu Val Ser Gly Cys Gly Thr Ala Ala Ala Leu Gln
20 25 30

Ser Ser Pro Ala Pro Gly His Asp Ala Arg Asn Val Gly Met Ala Ser
35 40 45

Gly Gly Gly Gly Gly Asp Ile Gly Thr Ser Asn Cys Ser Glu Ala Asp
50 55 60

Phe Leu Ala Thr Ala Thr Pro Val Lys Gly Asp Pro Gly Ser Phe Ile
65 70 75 80

Val Ala Tyr Gly Asn Arg Ser Asp Lys Thr Cys Thr Ile Asn Gly Gly
85 90 95

Val Pro Asn Leu Lys Gly Val Asp Met Ser Asn Ser Pro Ile Glu Asp
100 105 110

Leu Pro Val Glu Asp Val Arg Leu Pro Asp Ala Pro Lys Glu Phe Thr
115 120 125

Leu Gln Pro Gly Gln Ser Ala Tyr Ala Gly Ile Gly Met Val Leu Ala
130 135 140

Asp Ser Gly Asp Pro Asn Ala His Val Leu Thr Gly Phe Gln Ser Ser
145 150 155 160

Leu Pro Asp Met Ser Glu Ala Gln Pro Val Asn Val Leu Gly Asp Gly
165 170 175

Asn Val Lys Phe Ala Ala Lys Tyr Leu Arg Val Ser Ser Leu Val Ser
180 185 190

Thr Ala Asp Glu Leu Arg
195

<210> 24
<211> 751
<212> PRT
<213> Saccharopolyspora spinosa

<400> 24
Val Leu Ser Val Glu Lys Gly Arg Glu Ser Ala Thr Trp Thr Ala Val
1 5 10 15

BNSDOCID: <WO___9946387A1_I_>

Leu Glu Gly Thr Leu Glu Arg Ile Thr Phe Ala Asn Glu Glu Ser Gly
20 25 30

Tyr Thr Val Ala Arg Ile Asp Thr Gly Arg Gly Gly Asp Leu Val Thr
35 40 45

Val Val Gly Ala Leu Leu Gly Ala Gln Pro Gly Glu Ala Leu Arg Met
50 55 60

Arg Gly Arg Trp Gly Ser His Pro Gln Tyr Gly Arg Gln Phe His Val
65 70 75 80

Asp Asp Tyr Thr Thr Val Leu Pro Ala Thr Val Gln Gly Ile Arg Arg
85 90 95

Tyr Leu Gly Ser Gly Leu Ile Lys Gly Ile Gly Pro Lys Leu Ala Glu
100 105 110

Lys Ile Val Asp His Phe Gly Val Ala Ala Leu Asp Val Ile Glu Gln
115 120 125

Glu Pro Ala Arg Leu Ile Glu Val Pro Lys Leu Gly Pro Lys Arg Thr
130 135 140

Lys Leu Ile Ala Asp Ala Trp Glu Glu Gln Lys Ala Ile Lys Glu Val
145 150 155 160

Met Ile Phe Leu Gln Gly Val Gly Val Ser Thr Ser Leu Ala Val Lys
165 170 175

Ile Tyr Lys Gln Tyr His Asp Asp Ala Ile Arg Thr Val Lys Glu Glu
180 185 190

Pro Tyr Arg Leu Ala Gly Asp Val Trp Gly Ile Gly Phe Lys Thr Ala
195 200 205

Asp Thr Ile Ala Lys Ala Val Gly Ile Pro His Asp Ser Pro Gln Arg
210 215 220

Val Lys Ala Gly Leu Gln Phe Thr Leu Ser Glu Ser Thr Gly Asp Gly
225 230 235 240

Asn Cys Tyr Leu Pro Glu Asn Glu Leu Ile Ala Glu Ala Val Lys Ile
245 250 255

Leu Ala Val Asp Thr Gly Leu Val Ile Glu Cys Leu Ala Glu Leu Val
260 265 270

Thr Glu Glu Gly Val Val Arg Glu Glu Ile Pro Thr Asp Asp Asp Glu
275 280 285

Val Pro Thr Val Ala Ile Tyr Leu Val Pro Phe His Arg Ala Glu Val
290 295 300

Ala Leu Ala Asn Gln Leu Ser Arg Leu Leu Asn Thr Ser Ala Asp Arg
305 310 315 320

Met Pro Val Phe Ala Asp Val Asp Trp His Lys Ala Leu Asp Trp Leu

BNSDOCID: <WO___9946387A1_I_>

325 330 335

Arg Arg Ala Thr Gly Ala Glu Leu Ala Glu Ala Gln Glu Arg Ala Val
340 345 350

Lys Leu Ala Leu Thr Glu Lys Val Ala Val Leu Thr Gly Gly Pro Gly
355 360 365

Cys Gly Lys Ser Phe Thr Val Arg Ser Ile Ile Ala Leu Ala Gln Ala
370 375 380

Lys Lys Ala Lys Val Ile Leu Ala Ala Pro Thr Gly Arg Ala Ala Lys
385 390 395 400

Arg Leu Thr Glu Leu Thr Gly His Asp Ala Ala Thr Val His Arg Leu
405 410 415

Leu Gln Leu Gln Pro Gly Gly Asp Ala Ala Tyr Asp Arg Asp Asn Pro
420 425 430

Leu Asp Ala Asp Leu Val Val Val Asp Glu Ala Ser Met Leu Asp Leu
435 440 445

Leu Leu Ala Asn Lys Leu Ala Lys Ala Ile Ala Pro Gly Ala His Leu
450 455 460

Leu Leu Val Gly Asp Val Asp Gln Leu Pro Ser Val Gly Ala Gly Glu
465 470 475 480

Val Leu Arg Asp Leu Leu Ala Pro Gly Thr Pro Ile Pro His Val Arg
485 490 495

Leu Asn Glu Val Phe Arg Gln Ala Ala Glu Ser Gly Val Val Thr Asn
500 505 510

Ala His Arg Ile Asn Ala Gly Asp Tyr Pro Leu Thr His Gly Leu Thr
515 520 525

Asp Phe Phe Leu Phe His Val Glu Glu Ser Glu Pro Thr Ala Glu Leu
530 535 540

Thr Val Asp Val Val Ala Arg Arg Ile Pro Arg Lys Phe Arg Phe Asn
545 550 555 560

Pro Arg Thr Asp Val Gln Val Leu Ala Pro Met His Arg Gly Pro Ala
565 570 575

Gly Ala Gly Ala Leu Asn Gln Leu Leu Gln Glu Ala Ile Thr Pro Ala
580 585 590

Arg Glu Gly Leu Pro Glu Arg Arg Phe Gly Gly Arg Ile Phe Arg Val
595 600 605

Gly Asp Lys Val Thr Gln Ile Arg Asn Asn Tyr Asp Lys Gly Ala Asn
610 615 620

Gly Val Phe Asn Gly Thr Gln Gly Val Val Ser Ala Leu Asp Asn Glu
625 630 635 640

BNSDOCID: <WO___9946387A1_I_>

```
Ala Gln Thr Met Thr Val Arg Thr Asp Glu Asp Glu Asp Ile Asp Tyr
                645                 650                 655

Asp Phe Thr Glu Leu Asp Glu Leu Val His Ala Tyr Ala Val Thr Ile
            660                 665                 670

His Arg Ser Gln Gly Ser Glu Tyr Pro Cys Val Val Ile Pro Leu Thr
        675                 680                 685

Thr Ser Ala Trp Met Met Leu Gln Arg Asn Leu Leu Tyr Thr Ala Val
    690                 695                 700

Thr Arg Ala Lys Lys Val Val Val Leu Val Gly Ser Lys Lys Ala Leu
705                 710                 715                 720

Gly Gln Ala Val Arg Thr Val Gly Ser Gly Arg Arg His Thr Ala Leu
                725                 730                 735

Asp His Arg Leu Arg Arg Gly Gly Thr Gly Ser Arg Pro Ala Ala
            740                 745                 750
```

<210> 25
<211> 2310
<212> DNA
<213> Saccharopolyspora spinosa

<220>
<221> CDS
<222> (88)..(1077)

<220>
<221> CDS
<222> (1165)..(1992)

<400> 25

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ggatcctgct tcgtagctcg gtgtgtcatg ccagactgcg cacgcggacc tgcagcgggc 60

cgcgaaatcc cggcgaggaa gggcgcg atg cgg att ctg gtc acc ggc gga gcc 114
                              Met Arg Ile Leu Val Thr Gly Gly Ala
                                1               5

ggt ttc atc ggc tcg cac tac gtt cgg cag ttg ctc ggt ggt gcg tac   162
Gly Phe Ile Gly Ser His Tyr Val Arg Gln Leu Leu Gly Gly Ala Tyr
 10                  15                  20                  25

ccc gca ttc gcc gac gcc gac gtg gtc gtg ctc gac aag ctc acc tac   210
Pro Ala Phe Ala Asp Ala Asp Val Val Val Leu Asp Lys Leu Thr Tyr
                30                  35                  40

gcc ggc aac gag gcg aac ctg gcg ccg gtc gcg gac aac ccc cgg ctg   258
Ala Gly Asn Glu Ala Asn Leu Ala Pro Val Ala Asp Asn Pro Arg Leu
            45                  50                  55

aag ttc gtc tgc ggc gac atc tgc gac cgc gaa ctg gtt ggc ggc ctg   306
Lys Phe Val Cys Gly Asp Ile Cys Asp Arg Glu Leu Val Gly Gly Leu
        60                  65                  70
```


BNSDOCID: <WO___9946387A1_I_>

```
atg tcc ggc gtg gac gtg gtg gtg cac ttc gcc gcc gaa acc cac gtc   354
Met Ser Gly Val Asp Val Val Val His Phe Ala Ala Glu Thr His Val
     75                  80                  85

gac cgc tcg atc acc ggc tcg gac gcc ttc gtg atc acc aac gtg gtc   402
Asp Arg Ser Ile Thr Gly Ser Asp Ala Phe Val Ile Thr Asn Val Val
 90                  95                 100                 105

ggc acc aac gtg ctg ctg cag gcc gcg ctc gac gcc gag atc ggc aag   450
Gly Thr Asn Val Leu Leu Gln Ala Ala Leu Asp Ala Glu Ile Gly Lys
                110                 115                 120

ttc gtg cac gtt tcc acc gac gag gtc tac ggc tcc atc gag gac ggc   498
Phe Val His Val Ser Thr Asp Glu Val Tyr Gly Ser Ile Glu Asp Gly
            125                 130                 135

tcg tgg ccc gaa gac cac gcg ctg gag ccg aat tcc ccg tac tcg gcg   546
Ser Trp Pro Glu Asp His Ala Leu Glu Pro Asn Ser Pro Tyr Ser Ala
        140                 145                 150

gcg aaa gcg ggc tcg gac ctg ctg gcc cgc gcc tac cac cgc acc cac   594
Ala Lys Ala Gly Ser Asp Leu Leu Ala Arg Ala Tyr His Arg Thr His
    155                 160                 165

gga ctg ccg gtg tgc atc acc cgc tgc tcc aac aac tac ggg ccc tac   642
Gly Leu Pro Val Cys Ile Thr Arg Cys Ser Asn Asn Tyr Gly Pro Tyr
170                 175                 180                 185

cag ttc ccg gag aag gtg ctg ccg ctg ttc atc acg aac ctg atg gac   690
Gln Phe Pro Glu Lys Val Leu Pro Leu Phe Ile Thr Asn Leu Met Asp
                190                 195                 200

ggc agc cag gtg ccg ctc tac ggc gac ggg ctc aac gtg cgg gac tgg   738
Gly Ser Gln Val Pro Leu Tyr Gly Asp Gly Leu Asn Val Arg Asp Trp
            205                 210                 215

ctg cac gtc agc gac cac tgc cgg ggc atc cag ctg gtg gcc gac tcc   786
Leu His Val Ser Asp His Cys Arg Gly Ile Gln Leu Val Ala Asp Ser
        220                 225                 230

ggg cgc gcg ggc gag atc tac aac atc ggc ggc ggc acc gag ctg acc   834
Gly Arg Ala Gly Glu Ile Tyr Asn Ile Gly Gly Gly Thr Glu Leu Thr
    235                 240                 245

aac aac gag ctg acc gag cgg ctg ctg gca gag ctg ggc ctc gac tgg   882
Asn Asn Glu Leu Thr Glu Arg Leu Leu Ala Glu Leu Gly Leu Asp Trp
250                 255                 260                 265

tcg gtg gtg cgg ccg gtc acc gac cgc aag ggc cac gac cgc cgc tac   930
Ser Val Val Arg Pro Val Thr Asp Arg Lys Gly His Asp Arg Arg Tyr
                270                 275                 280

tcg gtg gac cac agc aag atc gtc gag gaa ctg ggg tac gcg ccg cag   978
Ser Val Asp His Ser Lys Ile Val Glu Glu Leu Gly Tyr Ala Pro Gln
            285                 290                 295

gtc gac ttc gag acc ggg ctg cgc gag aca atc cgc tgg tac cag gac   1026
```


BNSDOCID: <WO___9946387A1_I_>

```
Val Asp Phe Glu Thr Gly Leu Arg Glu Thr Ile Arg Trp Tyr Gln Asp
        300                 305                 310

aac cgg gac tgg tgg gag ccg ctg aag gcc cga tcg gcg gtg gct cga   1074
Asn Arg Asp Trp Trp Glu Pro Leu Lys Ala Arg Ser Ala Val Ala Arg
    315                 320                 325

tga gtcgcctcgc cgtgctggtt gcccggcggc cgcggccagc tgggctcgga        1127

330

gctggcccgg atcctcgccg cgcggacggg ggcgctg gtg cac cgg ccg ggt tcc  1182
                                    Val His Arg Pro Gly Ser
                                                335

ggg gaa ctg gac gtc acc gac gcc gag gag gtc gcc gac gcg ttg ggt   1230
Gly Glu Leu Asp Val Thr Asp Ala Glu Glu Val Ala Asp Ala Leu Gly
            340                 345                 350

tcc ttc gcg gag acg gcg aag gac gcg gag ctg cga ccg gtg gtg atc   1278
Ser Phe Ala Glu Thr Ala Lys Asp Ala Glu Leu Arg Pro Val Val Ile
        355                 360                 365

aac gcc gcg gcg tac acg gcg gtg gac gcg gcc gag tcc gac ccg gac   1326
Asn Ala Ala Ala Tyr Thr Ala Val Asp Ala Ala Glu Ser Asp Pro Asp
    370                 375                 380

cgc gcg gcc cgg atc aac gcc gaa ggc gcg gcc tcg ctg gcg aaa gcg   1374
Arg Ala Ala Arg Ile Asn Ala Glu Gly Ala Ala Ser Leu Ala Lys Ala
385                 390                 395                 400

tgc cgg agc agc ggt ctg ccc ctg gtg cac gtg tcg acg gat tac gtg   1422
Cys Arg Ser Ser Gly Leu Pro Leu Val His Val Ser Thr Asp Tyr Val
                405                 410                 415

ttc ccc cgt gat ggg gcc cgg ccg tac gag ccg acg gac ccg acc ggg   1470
Phe Pro Arg Asp Gly Ala Arg Pro Tyr Glu Pro Thr Asp Pro Thr Gly
            420                 425                 430

ccg cga tcg gtc tac ggg cgc acc aag ctc gaa ggc gaa cgg gcc gtg   1518
Pro Arg Ser Val Tyr Gly Arg Thr Lys Leu Glu Gly Glu Arg Ala Val
        435                 440                 445

ctg gag tcc ggc gcg cgg gcc tgg gtg gtg cgc acg gca tgg gtg tac   1566
Leu Glu Ser Gly Ala Arg Ala Trp Val Val Arg Thr Ala Trp Val Tyr
    450                 455                 460

ggc gcg agc ggc aag aac ttc ctg aaa acg atg atc cgc ctc tcg ggg   1614
Gly Ala Ser Gly Lys Asn Phe Leu Lys Thr Met Ile Arg Leu Ser Gly
465                 470                 475                 480

gag cgc gac acg ctg tcc gtt gtg gac aat cag atc ggc tcg ccg act   1662
Glu Arg Asp Thr Leu Ser Val Val Asp Asn Gln Ile Gly Ser Pro Thr
                485                 490                 495

tgg gcg gcg gac ctg gcg agc ggc ctg ctg gag ctg gcc gaa cgg gtc   1710
Trp Ala Ala Asp Leu Ala Ser Gly Leu Leu Glu Leu Ala Glu Arg Val
            500                 505                 510
```


BNSDOCID: <WO___9946387A1_I_>

```
gcc gaa cgc cgt gga ccg gag cag aag gtg ctg cac tgc acc aat tcc   1758
Ala Glu Arg Arg Gly Pro Glu Gln Lys Val Leu His Cys Thr Asn Ser
        515                 520                 525

ggc cag gtg acc tgg tac gag ttc gcg cgg gcg atc ttc gcg gaa ttc   1806
Gly Gln Val Thr Trp Tyr Glu Phe Ala Arg Ala Ile Phe Ala Glu Phe
    530                 535                 540

ggc ctg gac gag aac cgc gtc cac ccg tgc acg acg gcg gac ttc ccc   1854
Gly Leu Asp Glu Asn Arg Val His Pro Cys Thr Thr Ala Asp Phe Pro
545                 550                 555                 560

ctc ccg gcg cac cgc ccg gcc tac tcg gtc ctg tcc gac gtg gcg tgg   1902
Leu Pro Ala His Arg Pro Ala Tyr Ser Val Leu Ser Asp Val Ala Trp
                565                 570                 575

cga gag gcg ggc ctg acc ccg atg cgc acc tgg cgg gaa gcc ctg gcg   1950
Arg Glu Ala Gly Leu Thr Pro Met Arg Thr Trp Arg Glu Ala Leu Ala
            580                 585                 590

gcg gcc ttc gag aaa gac ggc gaa acc ctc cga acc cgc tga           1992
Ala Ala Phe Glu Lys Asp Gly Glu Thr Leu Arg Thr Arg
        595                 600                 605

ccagtcaccc ggagggcgcg agtagccccg gcagggccgt ttcgacgcga tatcggctgg 2052

cgcggtgcgc acaatgggtg tcgccggggc gaggaaggaa ggccaggtgc cccgggggca 2112

tgactgggag cctggcctga tgcctgtccg gggcgttcag cctgcggcga ggcggtatgc 2172

gttcagggtt gcttcggcgc aggttcgcca ggtgaaggct ttagcttggg cacggccctt 2232

ttccgcgtct gggggactgg tcagggcttg gtgcagggct tcgttgaggg ccgtcgggtc 2292

gccgtggggg aagcggat                                              2310
```

<210> 26
<211> 329
<212> PRT
<213> Saccharopolyspora spinosa

<400> 26

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Met Arg Ile Leu Val Thr Gly Gly Ala Gly Phe Ile Gly Ser His Tyr
  1               5                  10                  15

Val Arg Gln Leu Leu Gly Gly Ala Tyr Pro Ala Phe Ala Asp Ala Asp
             20                  25                  30

Val Val Val Leu Asp Lys Leu Thr Tyr Ala Gly Asn Glu Ala Asn Leu
         35                  40                  45

Ala Pro Val Ala Asp Asn Pro Arg Leu Lys Phe Val Cys Gly Asp Ile
     50                  55                  60

Cys Asp Arg Glu Leu Val Gly Gly Leu Met Ser Gly Val Asp Val Val
 65                  70                  75                  80
```


BNSDOCID: <WO___9946387A1_I_>

Val His Phe Ala Ala Glu Thr His Val Asp Arg Ser Ile Thr Gly Ser
85 90 95

Asp Ala Phe Val Ile Thr Asn Val Val Gly Thr Asn Val Leu Leu Gln
100 105 110

Ala Ala Leu Asp Ala Glu Ile Gly Lys Phe Val His Val Ser Thr Asp
115 120 125

Glu Val Tyr Gly Ser Ile Glu Asp Gly Ser Trp Pro Glu Asp His Ala
130 135 140

Leu Glu Pro Asn Ser Pro Tyr Ser Ala Ala Lys Ala Gly Ser Asp Leu
145 150 155 160

Leu Ala Arg Ala Tyr His Arg Thr His Gly Leu Pro Val Cys Ile Thr
165 170 175

Arg Cys Ser Asn Asn Tyr Gly Pro Tyr Gln Phe Pro Glu Lys Val Leu
180 185 190

Pro Leu Phe Ile Thr Asn Leu Met Asp Gly Ser Gln Val Pro Leu Tyr
195 200 205

Gly Asp Gly Leu Asn Val Arg Asp Trp Leu His Val Ser Asp His Cys
210 215 220

Arg Gly Ile Gln Leu Val Ala Asp Ser Gly Arg Ala Gly Glu Ile Tyr
225 230 235 240

Asn Ile Gly Gly Gly Thr Glu Leu Thr Asn Asn Glu Leu Thr Glu Arg
245 250 255

Leu Leu Ala Glu Leu Gly Leu Asp Trp Ser Val Val Arg Pro Val Thr
260 265 270

Asp Arg Lys Gly His Asp Arg Arg Tyr Ser Val Asp His Ser Lys Ile
275 280 285

Val Glu Glu Leu Gly Tyr Ala Pro Gln Val Asp Phe Glu Thr Gly Leu
290 295 300

Arg Glu Thr Ile Arg Trp Tyr Gln Asp Asn Arg Asp Trp Trp Glu Pro
305 310 315 320

Leu Lys Ala Arg Ser Ala Val Ala Arg
325

<210> 27
<211> 275
<212> PRT
<213> Saccharopolyspora spinosa

<400> 27
Val His Arg Pro Gly Ser Gly Glu Leu Asp Val Thr Asp Ala Glu Glu
1 5 10 15

BNSDOCID: <WO___9946387A1_I_>

```
Val Ala Asp Ala Leu Gly Ser Phe Ala Glu Thr Ala Lys Asp Ala Glu
            20                  25                  30

Leu Arg Pro Val Val Ile Asn Ala Ala Ala Tyr Thr Ala Val Asp Ala
        35                  40                  45

Ala Glu Ser Asp Pro Asp Arg Ala Ala Arg Ile Asn Ala Glu Gly Ala
    50                  55                  60

Ala Ser Leu Ala Lys Ala Cys Arg Ser Ser Gly Leu Pro Leu Val His
65                  70                  75                  80

Val Ser Thr Asp Tyr Val Phe Pro Arg Asp Gly Ala Arg Pro Tyr Glu
                85                  90                  95

Pro Thr Asp Pro Thr Gly Pro Arg Ser Val Tyr Gly Arg Thr Lys Leu
            100                 105                 110

Glu Gly Glu Arg Ala Val Leu Glu Ser Gly Ala Arg Ala Trp Val Val
        115                 120                 125

Arg Thr Ala Trp Val Tyr Gly Ala Ser Gly Lys Asn Phe Leu Lys Thr
    130                 135                 140

Met Ile Arg Leu Ser Gly Glu Arg Asp Thr Leu Ser Val Val Asp Asn
145                 150                 155                 160

Gln Ile Gly Ser Pro Thr Trp Ala Ala Asp Leu Ala Ser Gly Leu Leu
                165                 170                 175

Glu Leu Ala Glu Arg Val Ala Glu Arg Arg Gly Pro Glu Gln Lys Val
            180                 185                 190

Leu His Cys Thr Asn Ser Gly Gln Val Thr Trp Tyr Glu Phe Ala Arg
        195                 200                 205

Ala Ile Phe Ala Glu Phe Gly Leu Asp Glu Asn Arg Val His Pro Cys
    210                 215                 220

Thr Thr Ala Asp Phe Pro Leu Pro Ala His Arg Pro Ala Tyr Ser Val
225                 230                 235                 240

Leu Ser Asp Val Ala Trp Arg Glu Ala Gly Leu Thr Pro Met Arg Thr
                245                 250                 255

Trp Arg Glu Ala Leu Ala Ala Ala Phe Glu Lys Asp Gly Glu Thr Leu
            260                 265                 270

Arg Thr Arg
        275
```

<210> 28
<211> 1272
<212> DNA
<213> Saccharopolyspora spinosa

BNSDOCID: <WO___9946387A1_I_>

<220>
<221> CDS
<222> (334)..(1119)

<400> 28
aaggccaccg gcaaggtcgt gcagggcatc tcgcaggacg tcgcgaagaa gatctccaag 60

aagatccgcg acgagggccc gaagggcgtt caggcccaga tccagggcga gcagctgcgg 120

gtgtccggca agaagaagga cgacctgcag gccgtgatcc agttgctgaa gtcgagcgac 180

ttcgacgtcg cgctccagtt cgagaatttc cggtaatcca ccgctggagg tatccgggtg 240

aaggggatcg tgctggcggg tggcaacggg acccggctgc atccgctgac gcaggccgtg 300

tccaaacagc tacttccggt gtacgacaag ccg atg atc tac tac ccg ctg tcg 354
Met Ile Tyr Tyr Pro Leu Ser
1 5

gtg ctg atg ctg gcc ggc atc cgg gac gtg ctg ctg atc tcg acc ccg 402
Val Leu Met Leu Ala Gly Ile Arg Asp Val Leu Leu Ile Ser Thr Pro
10 15 20

gcc gac atg ccg ttg ttc cag cgg ctg ctc ggg aac ggg tcg cag ttc 450
Ala Asp Met Pro Leu Phe Gln Arg Leu Leu Gly Asn Gly Ser Gln Phe
25 30 35

ggc att cgg atc gag tac gcc gag cag tcc cag ccc aac ggg cta gcc 498
Gly Ile Arg Ile Glu Tyr Ala Glu Gln Ser Gln Pro Asn Gly Leu Ala
40 45 50 55

gag gcg ttc gtg atc ggt gcc gac ttc gtc ggc gac gac tcg gtg gcg 546
Glu Ala Phe Val Ile Gly Ala Asp Phe Val Gly Asp Asp Ser Val Ala
60 65 70

ttg gtg ctc ggc gac aac atc ttt tac ggg cag ggc ttt tcc ggg atc 594
Leu Val Leu Gly Asp Asn Ile Phe Tyr Gly Gln Gly Phe Ser Gly Ile
75 80 85

ctc cag cag tgc gtc cgg gag ctc gac ggc tgc acg ctg ttc ggc tac 642
Leu Gln Gln Cys Val Arg Glu Leu Asp Gly Cys Thr Leu Phe Gly Tyr
90 95 100

ccg gtc cgc gac ccg cag cgc tac ggc gtc ggt gag gtg gac gac gac 690
Pro Val Arg Asp Pro Gln Arg Tyr Gly Val Gly Glu Val Asp Asp Asp
105 110 115

ggt cgg ctg ttg tcc atc gtg gag aag ccg gag cgg ccg aag tcc aac 738
Gly Arg Leu Leu Ser Ile Val Glu Lys Pro Glu Arg Pro Lys Ser Asn
120 125 130 135

atg gcc atc acc ggc ctg tac ttc tac gac aac gac gtg gtg cgc atc 786
Met Ala Ile Thr Gly Leu Tyr Phe Tyr Asp Asn Asp Val Val Arg Ile
140 145 150

gcc aag ggg ctc acg ccg tcg gcc cgc ggc gag ctg gag atc acc gac 834
Ala Lys Gly Leu Thr Pro Ser Ala Arg Gly Glu Leu Glu Ile Thr Asp
155 160 165

BNSDOCID: <WO___9946387A1_I_>

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gtc aac ctg gcc tac ctg cag gag ggc cgg gcg cac ctg acc aag ctc   882
Val Asn Leu Ala Tyr Leu Gln Glu Gly Arg Ala His Leu Thr Lys Leu
        170                 175                 180

ggc cgc ggg ttc gcc tgg ctg gac acc ggg acc cac gac tcg cta gtg   930
Gly Arg Gly Phe Ala Trp Leu Asp Thr Gly Thr His Asp Ser Leu Val
    185                 190                 195

gag gcc tcg cag ttc gtg cag gtg ctg gag cac cgg cag ggc gtg cgg   978
Glu Ala Ser Gln Phe Val Gln Val Leu Glu His Arg Gln Gly Val Arg
200                 205                 210                 215

atc gcc tgc ctg gag gag atc ncc ctg cgc atg ggc tac atc tcg gcc   1026
Ile Ala Cys Leu Glu Glu Ile Xaa Leu Arg Met Gly Tyr Ile Ser Ala
                220                 225                 230

gac gac tgt ttc gcg ctg ggc gtg aag ctg gcc aag tcg ggc tac agc   1074
Asp Asp Cys Phe Ala Leu Gly Val Lys Leu Ala Lys Ser Gly Tyr Ser
            235                 240                 245

gag tac gtc atg gac gtc gcc cgc aac tcc ggc gcg cgg ggc tga       1119
Glu Tyr Val Met Asp Val Ala Arg Asn Ser Gly Ala Arg Gly
        250                 255                 260

cccgagctcg tccgatttcc attgaaatcg cggaccgtcg gcgtgtcgta gtccggtgcg 1179

ccgatattcc gggcggcgtc accaggccgg gggtagttgg tggccggcca tgccctccag 1239

gcggcgaaat gcggtcggcc atcggcgggt tgc                              1272
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<210> 29
<211> 261
<212> PRT
<213> Saccharopolyspora spinosa

<400> 29

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Met Ile Tyr Tyr Pro Leu Ser Val Leu Met Leu Ala Gly Ile Arg Asp
  1               5                  10                  15

Val Leu Leu Ile Ser Thr Pro Ala Asp Met Pro Leu Phe Gln Arg Leu
             20                  25                  30

Leu Gly Asn Gly Ser Gln Phe Gly Ile Arg Ile Glu Tyr Ala Glu Gln
         35                  40                  45

Ser Gln Pro Asn Gly Leu Ala Glu Ala Phe Val Ile Gly Ala Asp Phe
     50                  55                  60

Val Gly Asp Asp Ser Val Ala Leu Val Leu Gly Asp Asn Ile Phe Tyr
 65                  70                  75                  80

Gly Gln Gly Phe Ser Gly Ile Leu Gln Gln Cys Val Arg Glu Leu Asp
                 85                  90                  95

Gly Cys Thr Leu Phe Gly Tyr Pro Val Arg Asp Pro Gln Arg Tyr Gly
            100                 105                 110
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BNSDOCID: <WO___9946387A1_I_>

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Val Gly Glu Val Asp Asp Asp Gly Arg Leu Leu Ser Ile Val Glu Lys
        115                 120                 125

Pro Glu Arg Pro Lys Ser Asn Met Ala Ile Thr Gly Leu Tyr Phe Tyr
    130                 135                 140

Asp Asn Asp Val Val Arg Ile Ala Lys Gly Leu Thr Pro Ser Ala Arg
145                 150                 155                 160

Gly Glu Leu Glu Ile Thr Asp Val Asn Leu Ala Tyr Leu Gln Glu Gly
                165                 170                 175

Arg Ala His Leu Thr Lys Leu Gly Arg Gly Phe Ala Trp Leu Asp Thr
            180                 185                 190

Gly Thr His Asp Ser Leu Val Glu Ala Ser Gln Phe Val Gln Val Leu
        195                 200                 205

Glu His Arg Gln Gly Val Arg Ile Ala Cys Leu Glu Glu Ile Xaa Leu
    210                 215                 220

Arg Met Gly Tyr Ile Ser Ala Asp Asp Cys Phe Ala Leu Gly Val Lys
225                 230                 235                 240

Leu Ala Lys Ser Gly Tyr Ser Glu Tyr Val Met Asp Val Ala Arg Asn
                245                 250                 255

Ser Gly Ala Arg Gly
            260
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<210> 30

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

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<221> unsure

<222> (1)

<223> n is a, t, c, or g

<220>

<221> unsure

<222> (10)

<223> n is a, t, c, or g

BNSDOCID: <WO___9946387A1_I_>

<400> 30
ngsgtsggsn ssccaccttc cgg 23

<210> 31
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

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<221> unsure
<222> (6)
<223> n is a, t, c, or g

<220>
<221> unsure
<222> (18)
<223> n is a, t, c, or g

<400> 31
catsangtcg tcytcsansg csacgaacgc gtg 33

<210> 32
<211> 1165
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (226)..(834)

<220>
<223> Description of Artificial Sequence:pDAB1622

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cgcgtccttt ttggatcggg attgcggcag tacgtgcacc cggtttcagt gccccatttc 120

gcagtacgta cgtccgtttt gaatatggcg atcaatggct cgcatgaccc atatcaactc 180

BNSDOCID: <WO___9946387A1_I_>

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cgccccaccg aaccgcattc caaccaacgt cataggcttt cggcc gtg cag gta cgt 237
                                                 Val Gln Val Arg
                                                   1

cga ctt gac atc acg ggt gca tac gag ttc acc ccg aag gcc ttc ccc   285
Arg Leu Asp Ile Thr Gly Ala Tyr Glu Phe Thr Pro Lys Ala Phe Pro
  5                  10                  15                  20

gac cac cgg ggc ctg ttc gtg gcc ccg ttc cag gag gcg gcg ttc atc   333
Asp His Arg Gly Leu Phe Val Ala Pro Phe Gln Glu Ala Ala Phe Ile
                 25                  30                  35

gac gcc acg ggg cac ccg ctg cga gtc gcg cag acc aac cac agc gtc   381
Asp Ala Thr Gly His Pro Leu Arg Val Ala Gln Thr Asn His Ser Val
            40                  45                  50

tcg gcg cgc aac gtc atc cgc ggc gtg cac ttc tcg gac gtg ccg ccg   429
Ser Ala Arg Asn Val Ile Arg Gly Val His Phe Ser Asp Val Pro Pro
        55                  60                  65

ggc caa gcg aag tac gtg tac tgc ccg cag ggc gcg ctg ctc gac gtg   477
Gly Gln Ala Lys Tyr Val Tyr Cys Pro Gln Gly Ala Leu Leu Asp Val
    70                  75                  80

gtc atc gac atc cgg gtc ggt tcc ccg acc ttc ggc cgc tgg gag gcg   525
Val Ile Asp Ile Arg Val Gly Ser Pro Thr Phe Gly Arg Trp Glu Ala
 85                  90                  95                 100

gtc cgg ctc gac gac acc gag tac cgg gcc gtc tac cta gcc gaa gga   573
Val Arg Leu Asp Asp Thr Glu Tyr Arg Ala Val Tyr Leu Ala Glu Gly
                105                 110                 115

ctc ggg cac gcg ttc gcc gcg ctg acc gac gac acc gtg atg acc tac   621
Leu Gly His Ala Phe Ala Ala Leu Thr Asp Asp Thr Val Met Thr Tyr
            120                 125                 130

ctc tgc tcg acg ccc tac acc ccg ggc gcc gag cac ggc atc gac ccg   669
Leu Cys Ser Thr Pro Tyr Thr Pro Gly Ala Glu His Gly Ile Asp Pro
        135                 140                 145

ttc gac ccg gaa ctc gcg ttg ccg tgg tcc gac ctc gac ggt gaa ccg   717
Phe Asp Pro Glu Leu Ala Leu Pro Trp Ser Asp Leu Asp Gly Glu Pro
    150                 155                 160

gtc ctg tcc gaa aag gac cgg acc gcc ccg agc ctc gcg gaa gcc gcc   765
Val Leu Ser Glu Lys Asp Arg Thr Ala Pro Ser Leu Ala Glu Ala Ala
165                 170                 175                 180

gac aac ggc ctg ctt ccg gac tac gaa aca tgc ctc gcc cac tac gaa   813
Asp Asn Gly Leu Leu Pro Asp Tyr Glu Thr Cys Leu Ala His Tyr Glu
                185                 190                 195

ggc ctg cgc agc ccc ggc tga acggtcaccg caagcggccc ggcttcggcc      864
Gly Leu Arg Ser Pro Gly
            200

agaggcgcca ccggataatg ccgagcacct cggccgggcc gagctcccgc gagtccgtcg 924
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agccgaagtt gttgtcgccc tcgacgtacc agccatcgcc ctcgcggcgc agcgcgcgct 984

tcaccgacaa ctgccccggg cgctgggccc aacgcaccag cacgacgttt ccccggccgg 1044

gcggaacccc gaagccgcag cagcaccact tcgcgatccc gcagggtggg aaccataaac 1104

ggcccgcgca ccaccaaccg ccgccagggc cagcgcccga gggatttcac atccacctcc 1164

a 1165

<210> 33
<211> 202
<212> PRT
<213> Artificial Sequence

<400> 33

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Val Gln Val Arg Arg Leu Asp Ile Thr Gly Ala Tyr Glu Phe Thr Pro
  1               5                  10                  15

Lys Ala Phe Pro Asp His Arg Gly Leu Phe Val Ala Pro Phe Gln Glu
             20                  25                  30

Ala Ala Phe Ile Asp Ala Thr Gly His Pro Leu Arg Val Ala Gln Thr
         35                  40                  45

Asn His Ser Val Ser Ala Arg Asn Val Ile Arg Gly Val His Phe Ser
     50                  55                  60

Asp Val Pro Pro Gly Gln Ala Lys Tyr Val Tyr Cys Pro Gln Gly Ala
 65                  70                  75                  80

Leu Leu Asp Val Val Ile Asp Ile Arg Val Gly Ser Pro Thr Phe Gly
                 85                  90                  95

Arg Trp Glu Ala Val Arg Leu Asp Asp Thr Glu Tyr Arg Ala Val Tyr
            100                 105                 110

Leu Ala Glu Gly Leu Gly His Ala Phe Ala Ala Leu Thr Asp Asp Thr
        115                 120                 125

Val Met Thr Tyr Leu Cys Ser Thr Pro Tyr Thr Pro Gly Ala Glu His
    130                 135                 140

Gly Ile Asp Pro Phe Asp Pro Glu Leu Ala Leu Pro Trp Ser Asp Leu
145                 150                 155                 160

Asp Gly Glu Pro Val Leu Ser Glu Lys Asp Arg Thr Ala Pro Ser Leu
                165                 170                 175

Ala Glu Ala Ala Asp Asn Gly Leu Leu Pro Asp Tyr Glu Thr Cys Leu
            180                 185                 190

Ala His Tyr Glu Gly Leu Arg Ser Pro Gly
        195                 200
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<210> 34

BNSDOCID: <WO___9946387A1_I_>

<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 34
cccgaattcg agctgctgtc aatcaact 28

<210> 35
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 35
gggaagcttg ttgaccgtgg cggtttcct 29

<210> 36
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:mutagenic primer

<400> 36
ctggttcatt cggccgcctc accggtgggg atggccgcga tc 42

<210> 37
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:mutagenic primer

<400> 37
gatcgcggcc atccccaccg gtgaggcggc cgaatgaacc ag 42

<210> 38
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:flanking primer

<400> 38

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gctgctcgaa atcgcacgtc 20

<210> 39
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:flanking primer

<400> 39
gcatcgctgg gcagtgagg 19

BNSDOCID: <WO___9946387A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/03212

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/52 C12N15/70 C12N1/21 C12P19/62 C12Q1/68
C07K14/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N C12P C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATSUSHIMA P. ET AL.: "Conjugal transfer of cosmid DNA from Escherichia coli to Saccharopolyspora spinosa: effects of chromosomal insertions on macrolide A83543 production" GENE, vol. 146, 1994, pages 39-45, XP002106258 cited in the application see esp. p.43 part e. ---	1,3,5,7, 9,11,13, 15,16
A	BALTZ R H ET AL: "Molecular genetic methods for improving secondary-metabolite production in actinomycetes" TRENDS IN BIOTECHNOLOGY, vol. 14, no. 7, 1 July 1996, page 245-250 XP004035763 see esp. p.246 1.par - p.247 1.par; figure 1 --- -/--	1-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1999	30/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kania, T

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BNSDOCID: <WO___9946387A1_I_>

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/US 99/03212

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 13663 A (ABBOTT LAB) 22 July 1993 see the whole document	1-30
A	US 5 631 155 A (HUBER MARY L B ET AL) 20 May 1997 see the whole document	17-30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

BNSDOCID: <WO___9946387A1_I_>

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 99/03212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9313663 A	22-07-1993	CA 2100791 A	18-07-1993
		AU 665526 B	11-01-1996
		AU 1245092 A	03-08-1993
		EP 0626806 A	07-12-1994
US 5631155 A	20-05-1997	US 5591606 A	07-01-1997
		US 5767253 A	16-06-1997

BNSDOCID: <WO___9946387A1_I_>